INTERNALLY HYDROGEN-BONDED CHIRAL METHYLENENITRONES IN CYCLOADDITION REACTIONS

BY

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26-2-2006

لاَ يُسْتَطَاعُ الْعِلْمُ بِرَاحَةِ الْجِسْمِ

[يَحْيَى بْنِ أَبِي كَثِيرٍ]

DEDICATED TO

MY PARENTS AND FAMILY

ACKNOWLEDGMENTS

First and foremost thanks to Allah who gave me strength, patience and ability to accomplish this research.

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التخصـــــص: الكيمياء

تاريخ التخـــرج : يناير ٢٠٠٦ م

تمت دراسة الإضافة الحلقية ١،٣- ثنائية القطب لاثنين من الميثلين نيترون غير متماثلة (chiral) وهي :
(*R*)-*N*-2-(1-hydoxy-2-phenyl ethyl)methylenenitrone (I) و
(1*R*,2*S*,3*R*,4*R*)-*N*-3-(2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptanyl)methylenenitrone(II)
مع ألكينات آحادية و ثنائية و ثلاثية. ولقد أظهر النيترون (II) انتقائية وجهيةً و اتجاهيةً أفضل. تم تفسير الناتج الكيميائي الاتجاهي لهذه التفاعلات بناء على العوامل الفراغية و التداخلات المدارية الثانوية للمركبات الانتقالية. كما تم إظهار مدى تاثير الرابطة الهيدروجينية الداخلية ضمن الجزيئ الواحد.

ولقد أظهرت الإضافة الحلقية ثنائية القطب للنيترون (I) باستخدم مجنيزيوم البروميد انتقائية اتجاهية و مكانية متميزة. ولقد بررت الإنتقائية المُحسَّنة باستعمال شكلٍ حلقي لمعقد النيترون مع الفلز.

إن النتائج التي توصلت هذه الدراسة ستكون حقا ذات أهمية في تصنيع المراكز غير متماثلة (chiral centers) للمنتجات الطبيعية.

درجة الماجستير في العلوم

جامعة الملك فهد للبترول والمعادن

الظهران، المملكة العربية السعودية

يناير ٢٠٠٦ م

THESIS ABSTRACT

NAME : Muhammad Zaki Nur Iman
TITLE : Internally hydrogen-bonded chiral methylenenitrones in cycloaddition reactions
MAJOR : Chemistry
DATE : January, 2006

1,3-Dipolar cycloaddition (DC) reactions of two chiral methylene nitrones, (*R*)-*N*-2-(1-hydoxy-2-phenyl ethyl)methylenenitrone (I) and (1*R*,2*S*,3*R*,4*R*)-*N*-3-(2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptanyl)methylenenitrone (II), with a multitude of mono-, di-, and tri-substituted alkenes have been studied in detail. The nitrone (II) showed better face and stereoselectivity. The stereochemical outcome has been explained in terms of steric factors and secondary orbital interactions in the transition states. The effect of intramolecular hydrogen bonding has also been demonstrated.

The DC reactions of the nitrone (I) in the presence of magnesium bromide have exhibited remarkable regio- and stereoselectivity. The improved selectivity has been rationalized using a metal chelated cyclic form of the nitrone.

The findings of the study would indeed be useful in incorporating chiral centers in natural product synthesis.

Master of Science Degree
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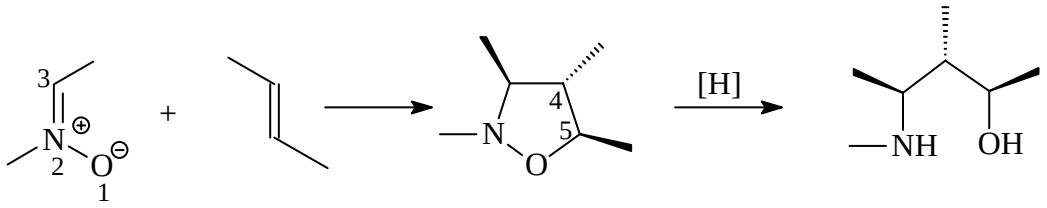
CHAPTER 1

INTRODUCTION

The 1,3-Dipolar Cycloaddition (DC) reactions of nitrones **1** with alkenes **2** leading to isoxazolidines **3** is a fundamental reaction in organic chemistry, and the available literature on this topic of organic chemistry is vast. In this reaction, up to three contiguous asymmetric centers can be formed as outlined for the reaction between nitrone **1** and a 1,2-disubstituted alkene **2** (Scheme 1). The relative stereochemistry at C-4 and C-5 is always controlled by the geometric relationship of the substituents on the alkene.

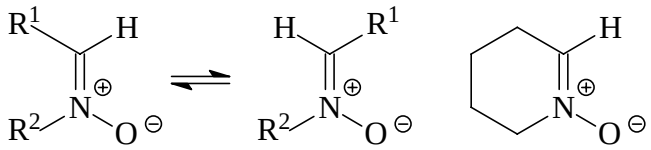
1,3-DC reactions of nitrones with alkenes have found general application in organic synthesis. The major reason for the synthetic utility of this reaction is the variety of attractive compounds which are available from isoxazolidines **3**. Important amino alcohols **4** can be obtained from isoxazolidines upon reduction, with retention of the configuration at the chiral centers (scheme 1).



1 **2** **3** **4**

Scheme 1

The cyclic nitrones, in the absence of E ⇔ Z isomerization enjoy higher degree of stereoselectivity in comparation to its acyclic counterparts where the stereochemical outcome is complicated by the E ⇔ Z isomerization prior to cycloadditions (scheme 2). However, it is often difficult to convert the cycloadducts from cyclic nitrones to synthetically important acyclic products. It is our objective to design acyclic nitrones (i) which would have two different fixed faces by virtue of H-bonding (Scheme 3) and as such would enjoy the selectivity inherent in a cyclic nitrone (ii) and which being unsubstituted at the carbon terminal of the nitrone would not be involved in E ⇔ Z isomerization.



E ***Z*** ***E***

5 **6**

Scheme 2

Following are the objectives of the proposed study:

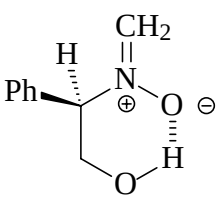
A. Synthesis of two chiral nitrones **7** and **8** (scheme 3).

B. Study of the asymmetric induction in the 1,3-Dipolar cycloaddition reactions of the chiral nitrones with a multitude of alkenes (Schemes 4, 5).

C. Study of the effect of metal-ion mediated cycloaddition on the asymmetric induction

D. Conversion of the cycloaddition products to synthetically important chiral intermediates (Scheme 6).

E. Characterization of the synthesized compounds using various spectroscopic techniques and structure determination by X-ray analysis.



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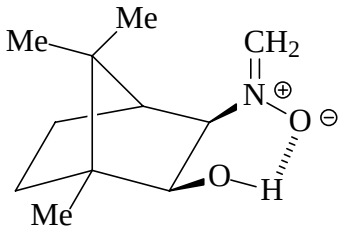

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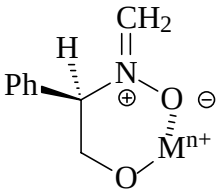

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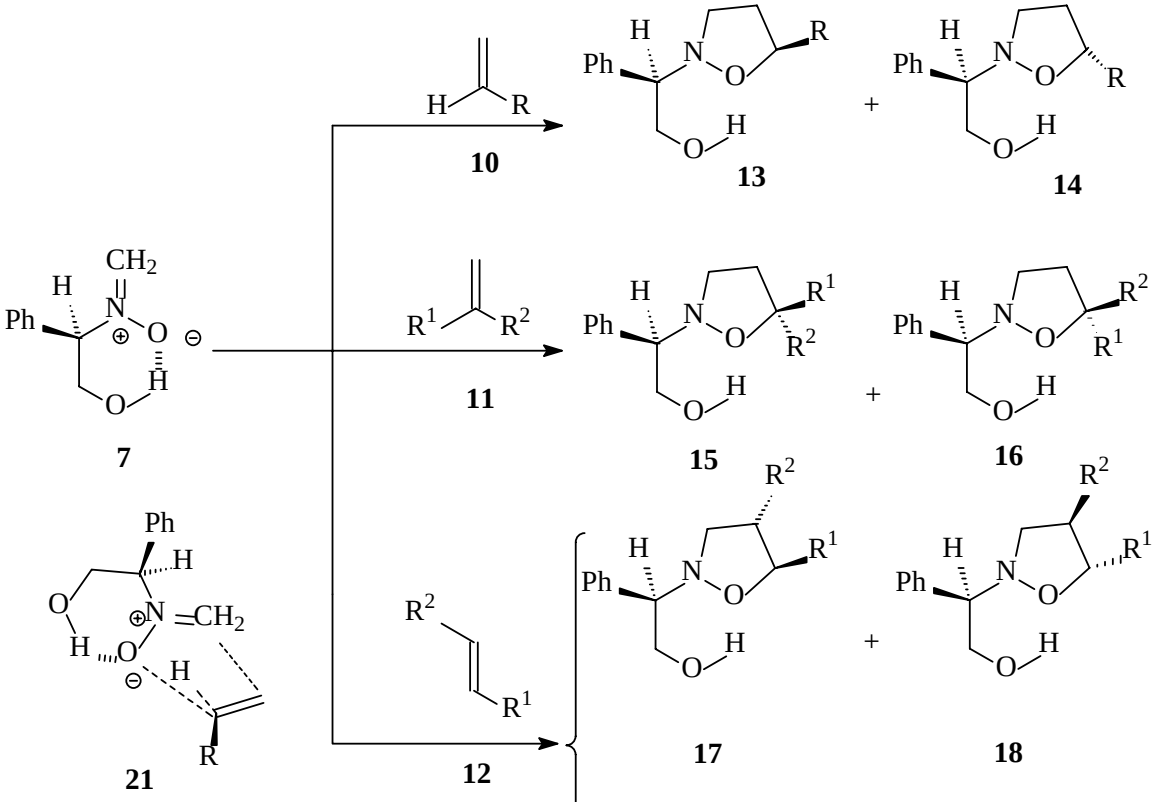
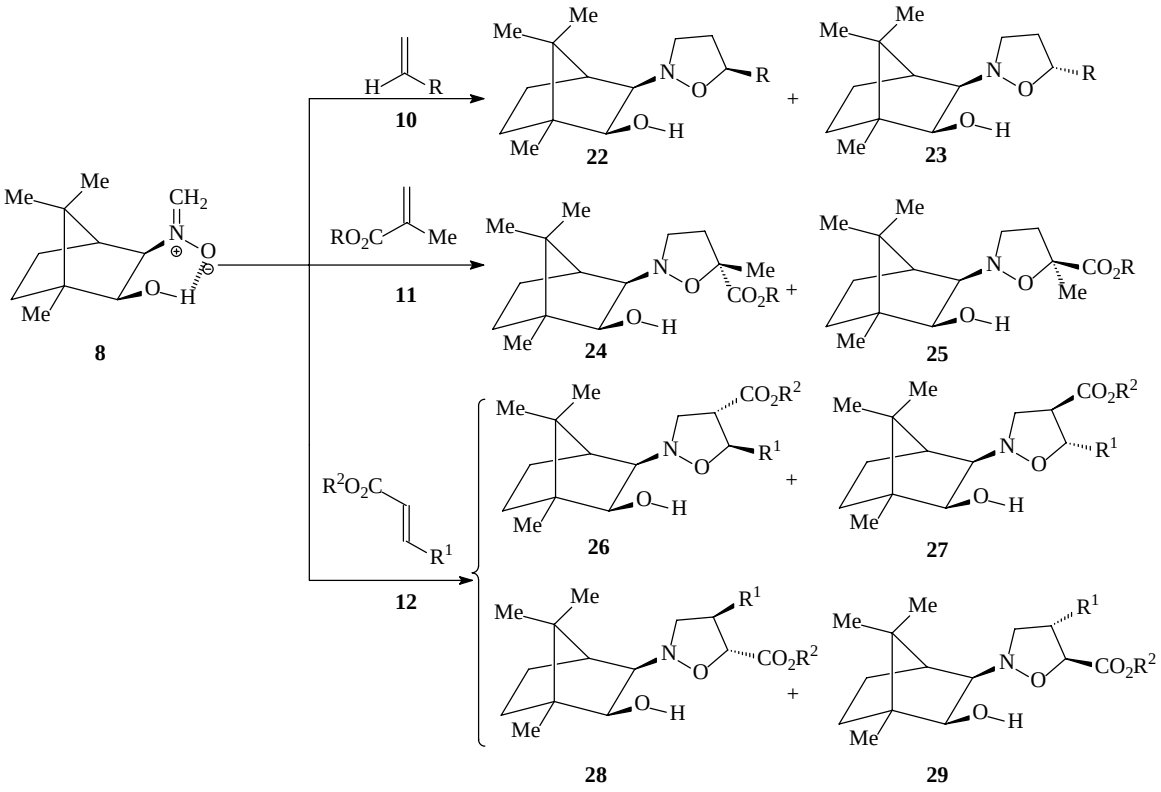
Scheme 3

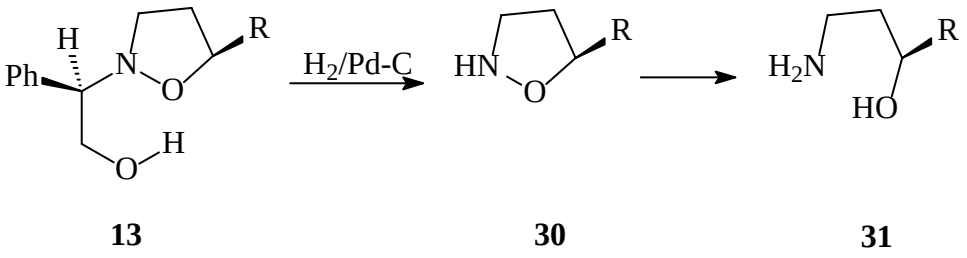


Favored transition state:
exo-oriented R
α–face of the nitrone

Scheme 4



Scheme 5



Scheme 6

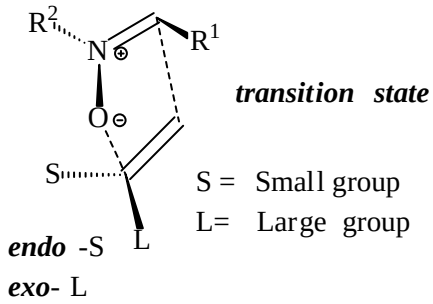
CHAPTER 2

LITERATURE REVIEW

Among a plethora of functional groups, nitrone functionality has etched an important place in organic chemistry.[1,2] This was possible largely owing to the brilliant efforts of Huisgen[3,4] and LeBel[5] who explored systematically the inter- and intra-molecular 1,3-dipolar cycloaddition reactions, respectively. Nitrone cycloaddition is indeed the best chemical template for constructing isoxazolidine ring systems in high yields. Even though the nitrone functionality was known in the last century, Tufariello[6] has made pioneering applications of the nitrone cycloaddition in the synthesis of natural products in the seventies. Since then both inter- and intra-molecular additions involving cyclic and acyclic nitrones have led to the synthesis of a variety of natural products of biological interest.[1,2] Remarkable regio- and stereoselectivity along with efficient incorporation of multiple stereocenters have made the cycloaddition an attractive key step in many a total synthesis.

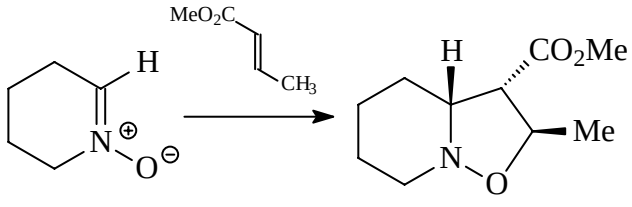
Regio- and stereo-chemical details and reactivity phenomenona associated the addition reactions of several parent carbo- and heterocyclic nitrones with a variety of alkenes have been studied[7-15] in some detail.

With the normal and electron-rich mono- and 1,1-disubstituted alkenes, the cycloadditions result in the regiospecific formation of products (cycloadducts) with oxygen terminal of the nitrone attaching itself to the more substituted end of the alkene (Scheme 7). However, with electron-deficient alkenes, usually a regioisomeric mixture of adducts are obtained; and in some cases complete reversal in the regioselection is observed.[16] While the steric factor dictates the approach of the alkene with *exo*-oriented large group L (to avoid steric interaction with the R^2 group), the favorable secondary orbital interactions may even force the L group to have *endo* orientation provided that L is an electron withdrawing conjugated substituent (Scheme 7).



Scheme 7

The 1,3-dipolar cycloaddition reaction between a cyclic nitrone and an olefin allows up to three contiguous stereocenters to be created in a single step as decribed[17] in the reaction between the cyclic nitrone **32** and methyl crotonate which affords the cycloadduct **33** as the predominant product. The favorable transition state has the carbomethoxy group *endo*-oriented, so that it can demonstrate secondary orbital interactions involving the overlap of the π-orbitals of the nitrone and alkene (Scheme 8).



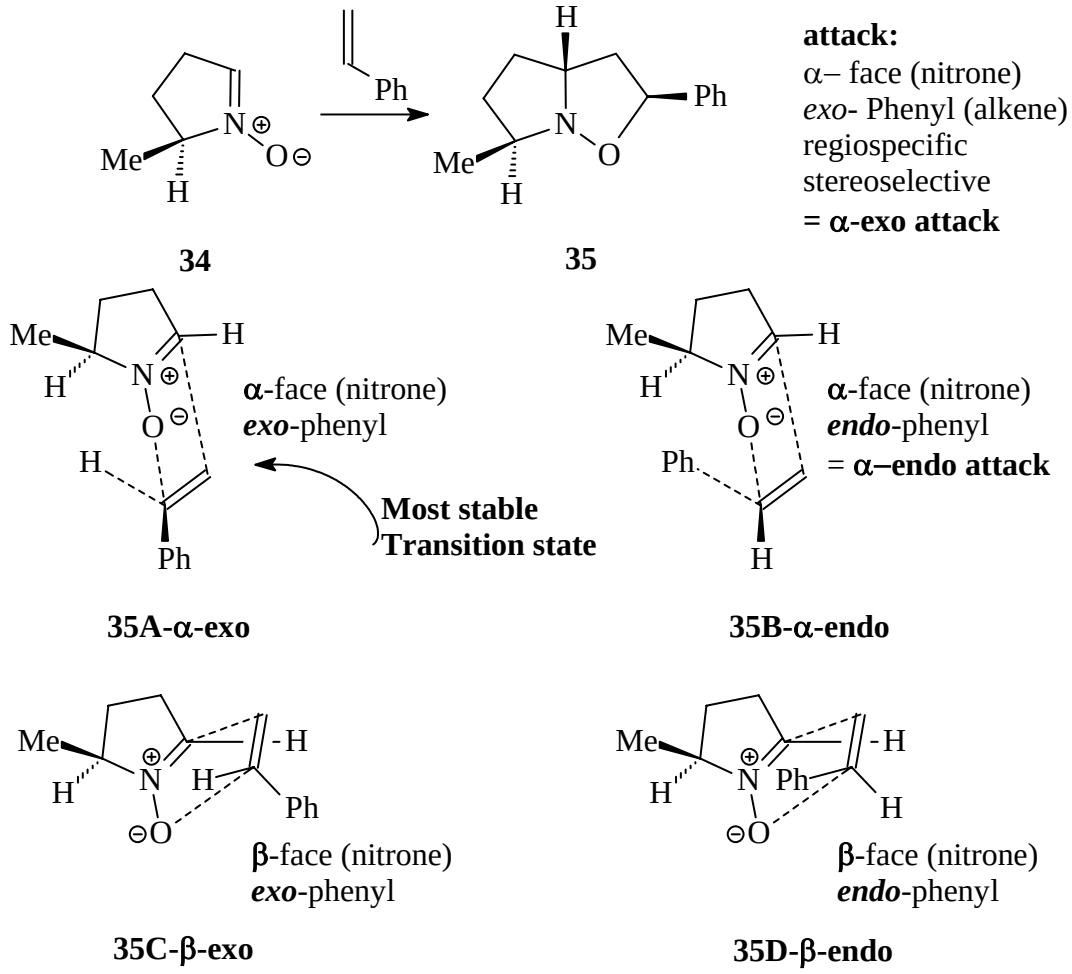
32 **33**

α-*endo*(CO_2Me) attack

The structure **33** is a result of *endo*-oriented CO_2Me approaching the **α-face** of the nitrone

Scheme 8

The five-membered cyclic nitrone **34** was found to undergo[18] face selective, regiospecific, and stereoselective addition reaction with styrene to give the cycloadduct **35** exclusively *via* the sterically favored transition state **35A** as depicted in the Scheme 9.



Scheme 9

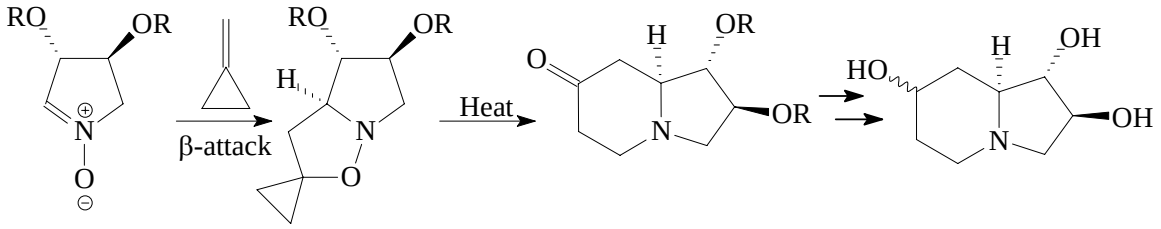
The development of 1,3- dipolar nitrone cycloaddition has in recent years entered a new stage, as control of the stereochemistry has now become the major challenge. The selectivity challenge is to control the regio-, diastereo- and enantioselectivity of the reaction. Dipolar cycloaddition reactions are among the most important tools for synthesis in organic chemistry, particularly for the formation of compounds with new chiral centers. Asymmetric syntheses were given a growing importance in the pharmaceutical industries with respect to the preparation of chiral drugs and natural products.[19,20] There have been

much interest in the asymmetric synthesis of isoxazolidines using 1,3-dipolar cycloaddition reaction.[21,22] Intermolecular nitrone olefin cycloaddition reaction leading to optically active isoxazolidines have been carried out by several workers using chiral starting material (nitrone or alkene or both) and by metal-catalyzed reactions. Several groups have also reported intramolecular reaction of alkenyl nitrone leading to optically active products.[21]

2.1. Intermolecular 1,3-DC reactions involving chiral nitrones and achiral alkenes

2.1.1. 1,3-DC reactions of chiral cyclic nitrones

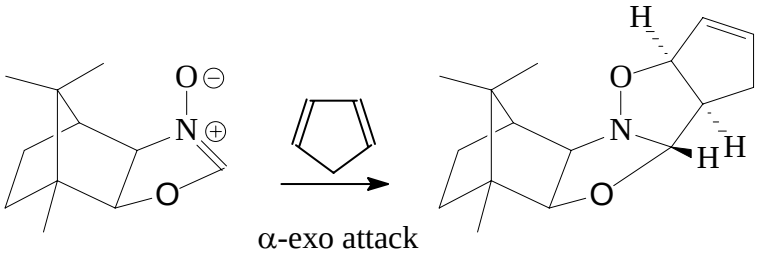
Cycloaddition reactions employing methylenecyclopropane and nitrone **36,** derived from an enantiomerically pure L-tartaric acid, followed by reduction of the intermediate indolizidinone **38** and final deprotection yielded two epimeric products **39** (Scheme 10).[23] Both epimers demonstrated high inhibiting abilities toward the enzymes glycosidases.



36 **37** **38** **39**

Scheme 10

Langlois et al.[24] applied the nitrone cycloaddition reaction in a highly regio- and diasteroselective manner involving **40** and cyclopetandiene to generate **41** as an intermediate in the synthesis of (-)-carbovir, a potential agent in treating AIDS (Scheme 11).

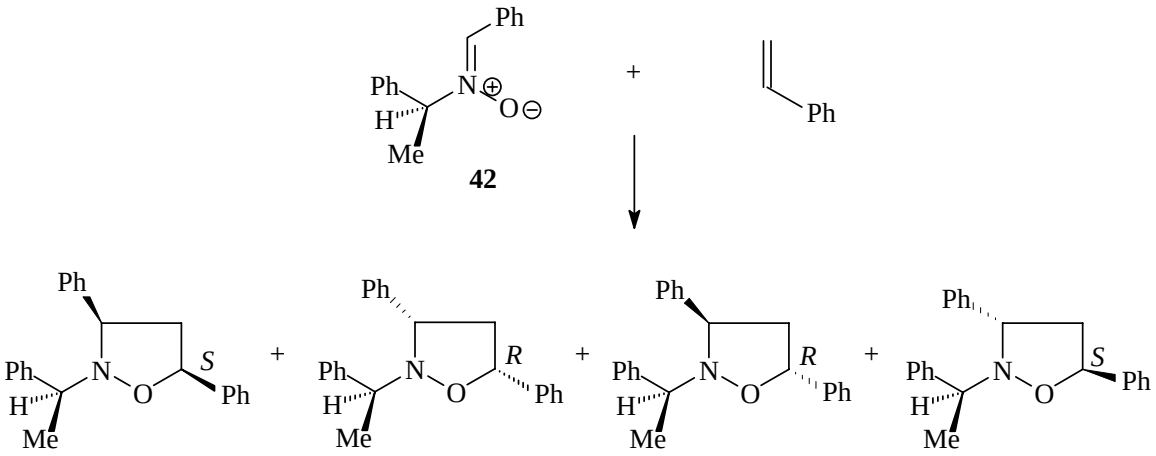


40 **41**

Scheme 11

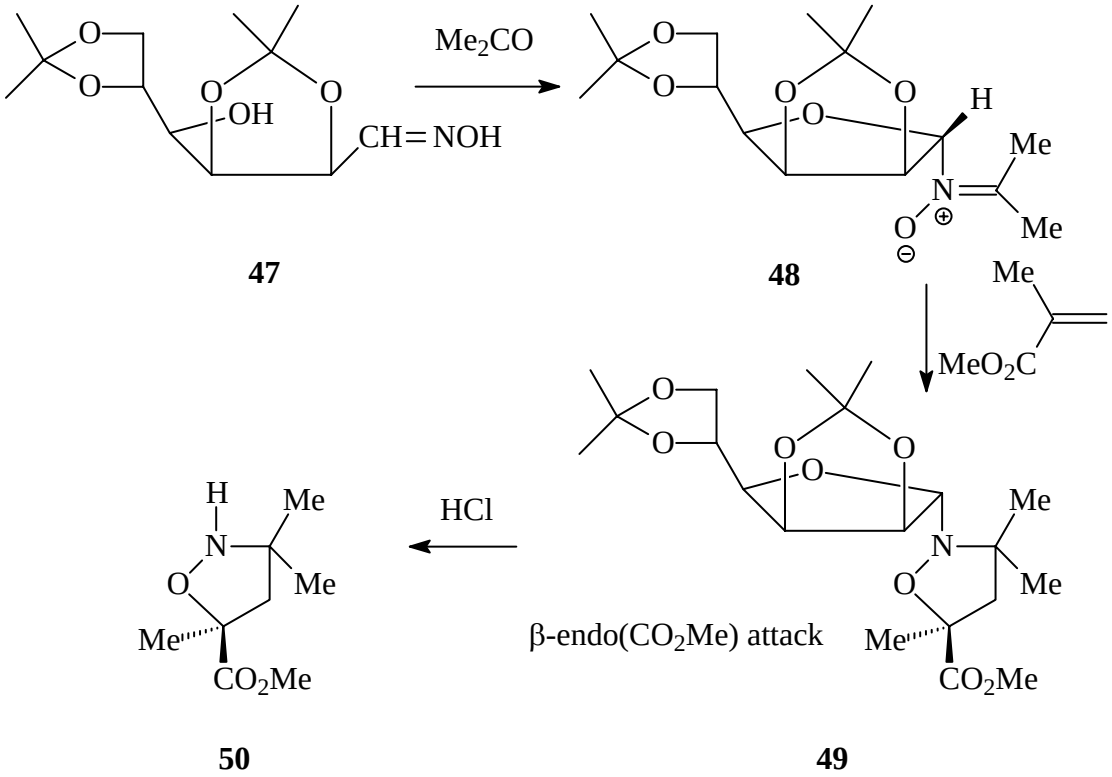
2.1.2. 1,3-DC reactions of nitrones having chiral substituent located on the nitrogen terminal of the nitrone

The pioneering work in the late 1970's by Belzecki, Vasella and their coworkers[25,26] demonstrated that relatively simple chiral substituents attached to the nitrone either through nitrogen or carbon resulted in the formation of optically active isoxazolidines upon cycloaddition with an achiral alkene. Diastereomeric excess depends largely upon the choice of chiral substituents. When the chiral aldonitrone **42**, containing 1-phenylethyl substituent at the nitrogen atom was subjected to undergo the 1,3-dipolar cycloaddition reaction with styrene (Scheme 12), the reaction proceeded to give a mixture of *diastereomers* **43-46** in a ratio of 76 : 11 : 8 : 5, respectively.



Scheme 12

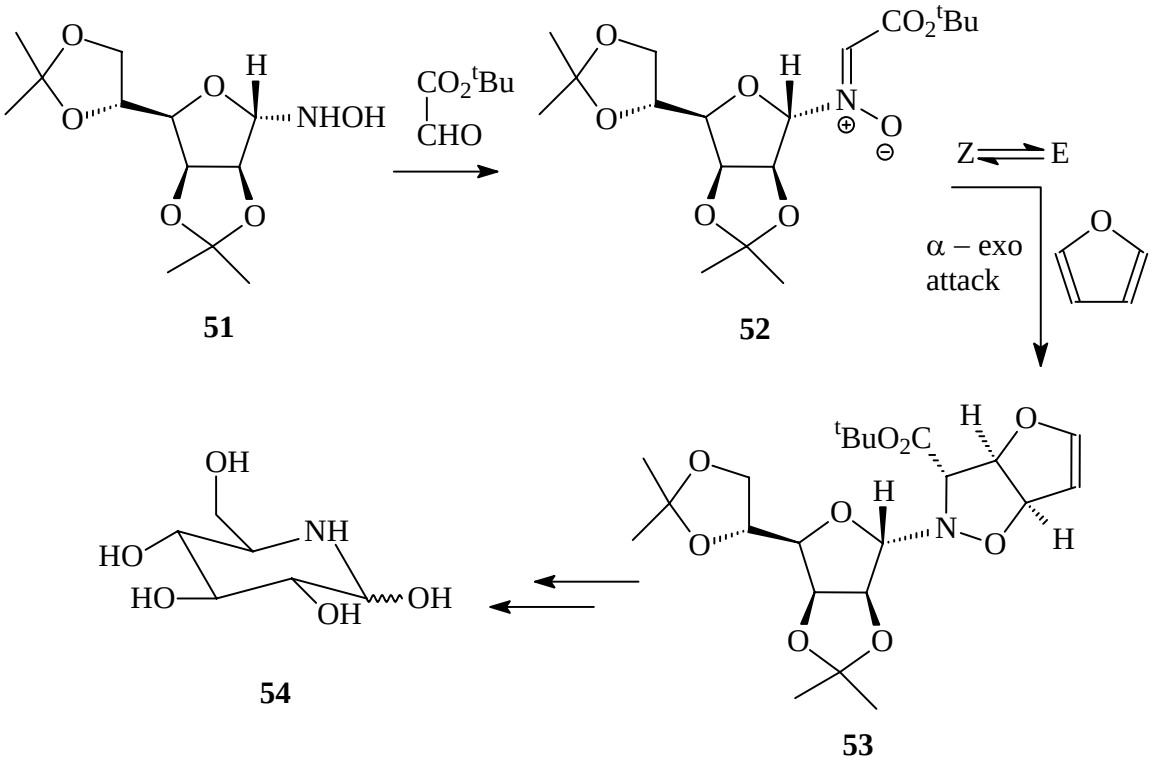
The optically active nitrone **47** derived from partially protected D-mannose oxime **48** gave the isoxazolidine **49** as a mixture of two diastereomers which on hydrolysis afforded the isoxazolidine **50** with 90% ee[27,28] (Scheme 13).



Scheme 13

Vassela's excellent and extensive work involving the use of furanosides and pyranoside hydroxylamines as nitrone precursor allowed the synthesis of several interesting biologically active molecules including nucleosides, proline, nojirimycin and captopril; the high diastereoselectivity (up to 90%) noted in the cycloaddition steps of these synthesis being attributed to the influence of a kinetic anomeric effect.[28]

In one example, the nitrone **52** derived from D-mannosyl derivative **51** reacted with furan afforded the isoxazolidine **53** exclusively (38%) which was then transformed to (+)nojirimycin **54** (Scheme 14).[29]

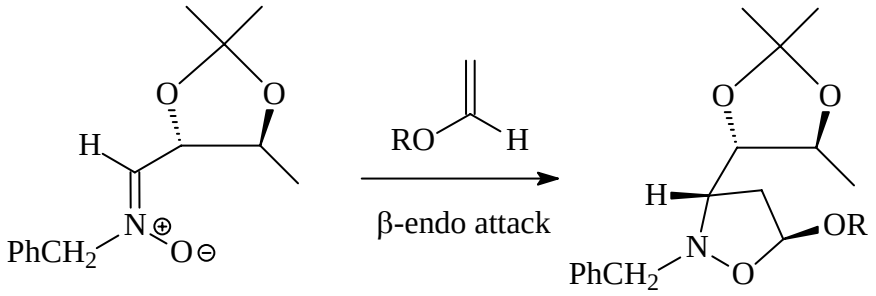


Scheme 14

2.1.3. 1,3-DC reactions of nitrones having chiral substituent located on the carbon terminal of the nitrone

Brandi *et al* have used optically active nitrones, having chiral moiety located at the carbon atom, in the cycloaddition reaction with prochiral mono olefins. The reaction shows poor to excellent diastereofacial selectivity.[30]

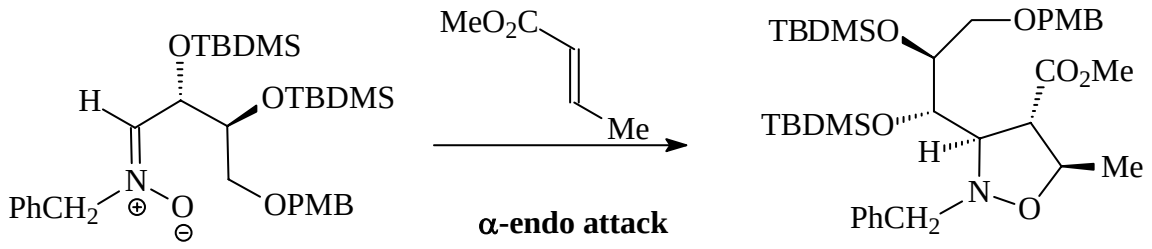
A racemate of the nitrone **55** has been used in a reaction with vinyl ethers or esters to give the cycloadduct **56** (Scheme 15) in excellent diastereomeric excess.[31]



55 **56**

Scheme 15

A tartaric acid derived nitrone **57** has been developed[32] that undergoes addition reaction with methyl crotonate to give the cycloadduct **58** in an *endo* (CO_2Me)/*exo* ratio of 10:1 and with a high diasterofacial induction of the *endo* isomer (Scheme 16).



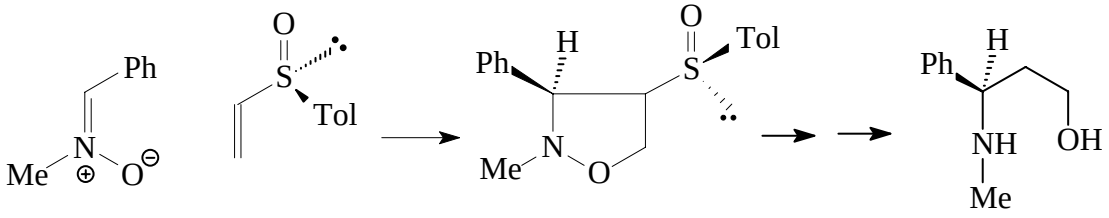
57 **58**

Scheme 16

2.2. Intermolecular 1,3-DC reactions involving achiral nitrones and chiral alkenes

Asymmetric induction in nitrone cycloaddition reaction using chiral alkenes has been studied by several groups. The alkenes employed were mostly (i) chiral allylic alcohol, (ii) chiral allylic amines, (iii) chiral vinyl sulfoxides (Scheme 17) or vinyl

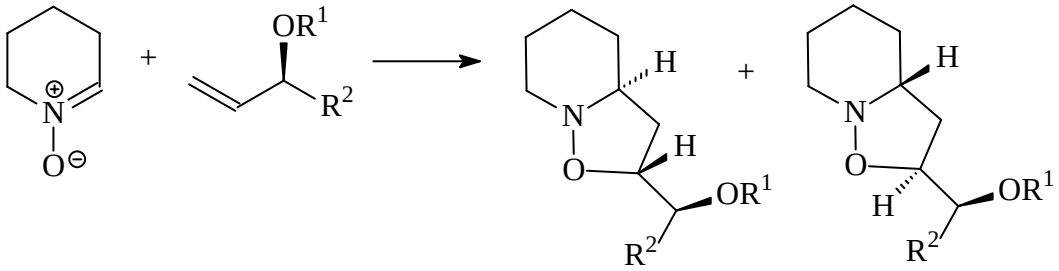
phosphine oxides. The *exo:endo* selectivity and diastereofacial selectivity were found to be modest to excellent.[33]



59 **60** **61** **62**

Scheme 17

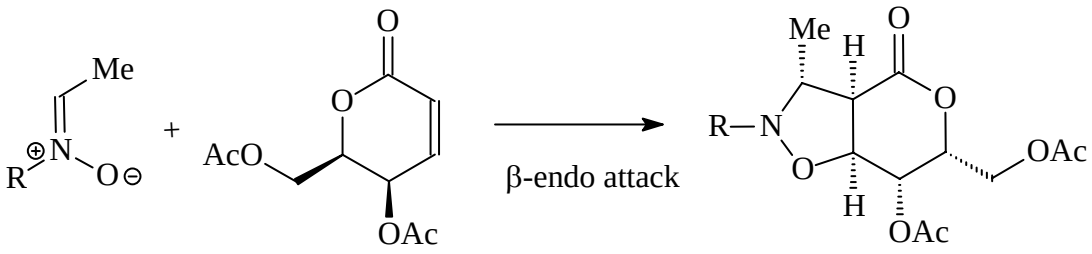
Kibayashi et al.[34,35] have used enantiomerically pure allylic ethers/alcohols in addition reaction with cyclic nitrone **32** to synthesize optically active alkaloids (Scheme 18). The reactions give mostly the *exo*-adducts with minor amount of the *endo* isomers.



32 **63** β-exo attack **64** α-exo attack

Scheme 18

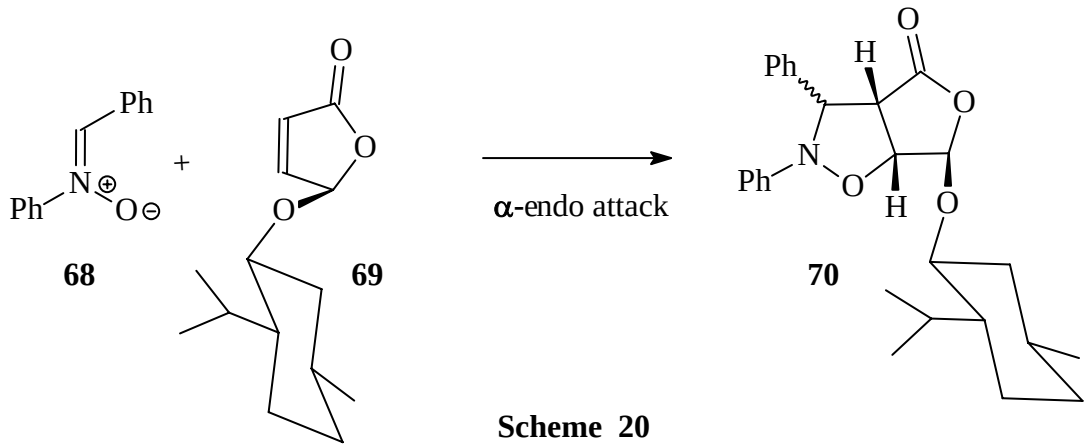
C-Methyl nitrones **65** approach the lactone **66** in an *endo*-selective manner to the face of the alkene *anti* to the substitiuents in the ring to give the cycloadduct **67** as the sole isomer[36](Scheme 19).



65 **66** **67**

Scheme 19

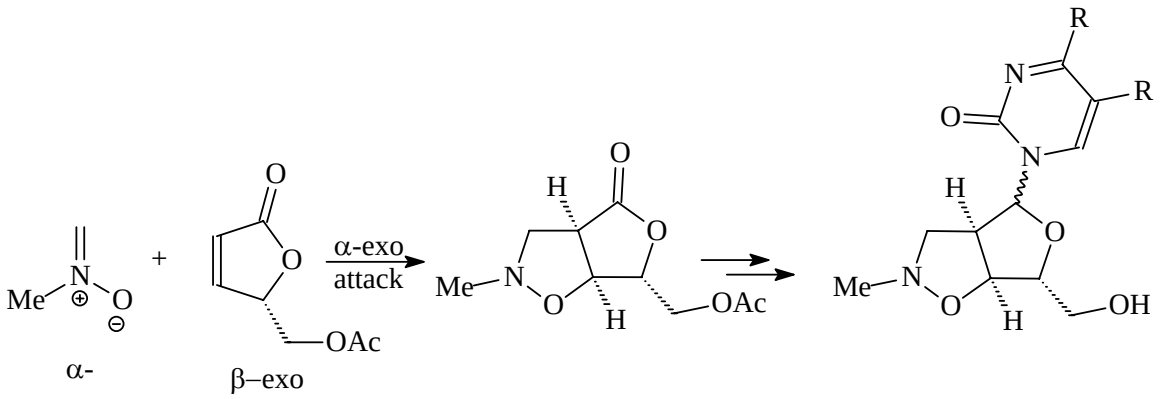
In the reaction of the lactone **69** with C,N-diphenylnitrone **68**, one face of the alkene is selectively shielded by the menthol moiety, leading exclusively to the anti adduct **70** as a 65:35 mixture of the *exo*- and *endo* isomers, respectively[37] (Scheme 20).



68 **69** **70**

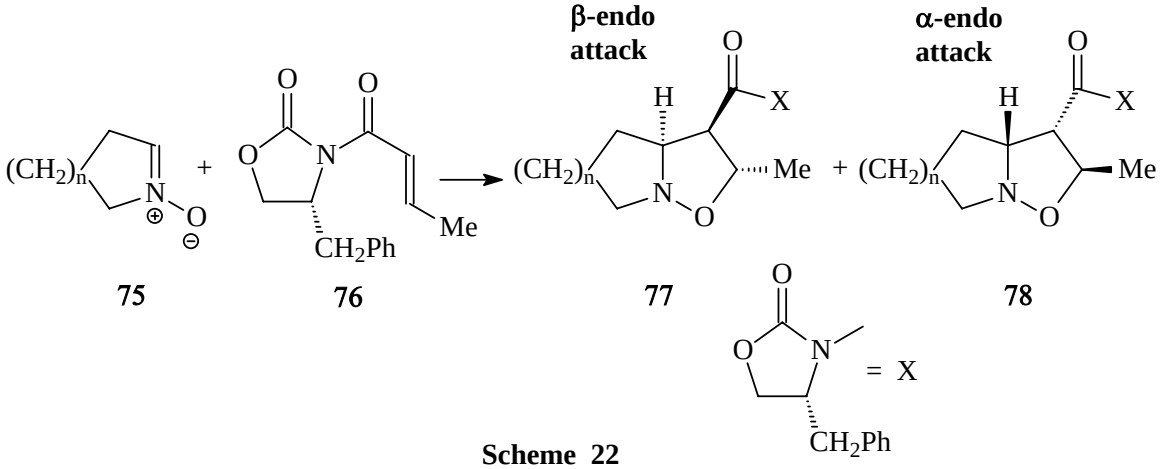
Scheme 20

The following DC reaction has been used to synthesise isoxazolidinyl nucleosides as part of a program aimed at the synthesis of novel anti-HIV agents (Scheme 21). The reaction afforded a single isoxazolidine **73** in excellent yield. Subsequent manipulation afforded the pyrimidine nucleoside analogue **74**.[38]



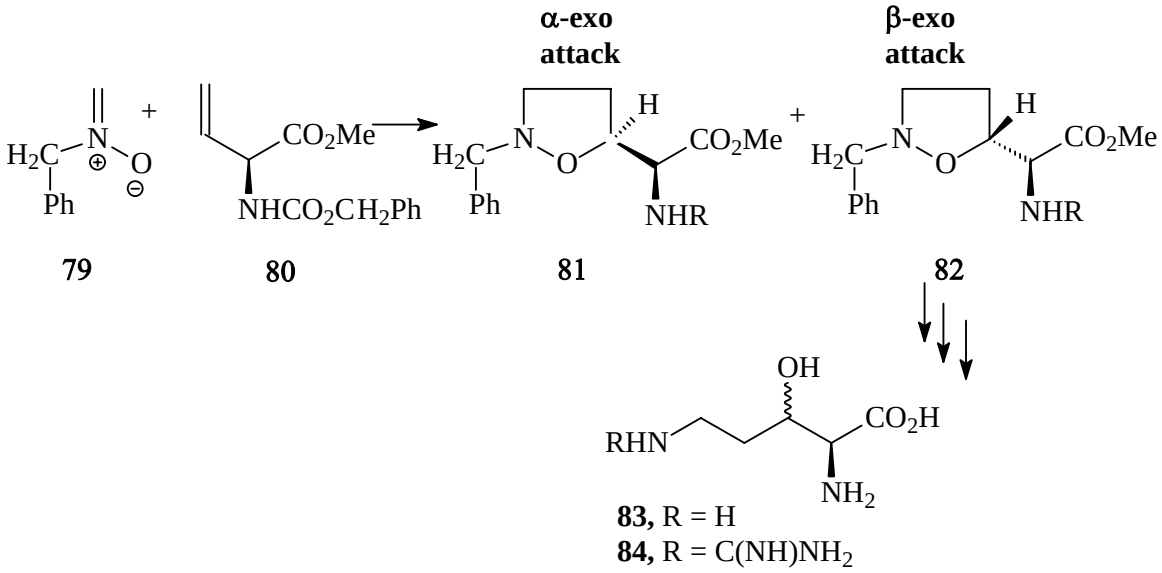
Scheme 21

Murahashi has utilized chiral α,β-unsaturated amides[39] and obtained a mixture of *endo*(CO_2R)-adducts **77, 78** in excellent yield (Scheme 22).



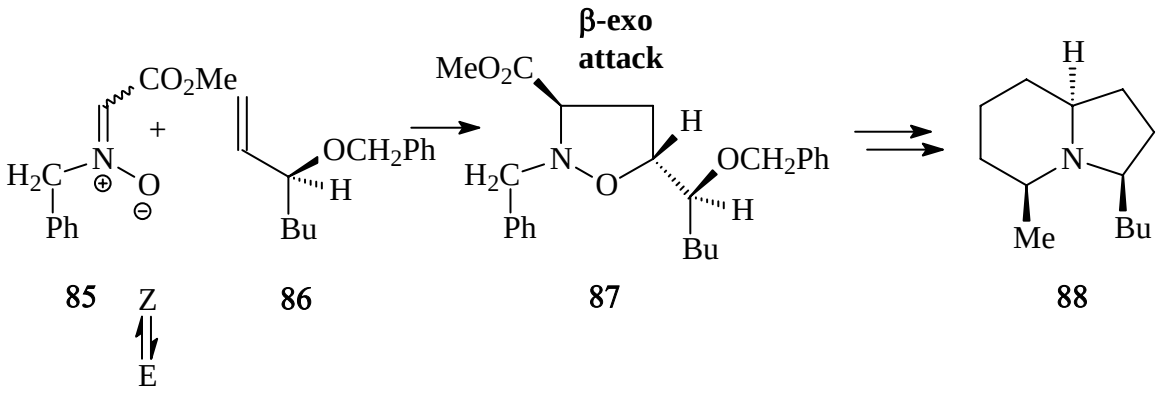
Scheme 22

Synthetic utility of chiral vinyglycine was employed in the synthesis of (3R)- and (3S)-hydroxyorthinine **83** and arginine **84** *via* the cycloaddition products **81** and **82** obtained in a ratio of 2:3, respectively (Scheme 23).[40]



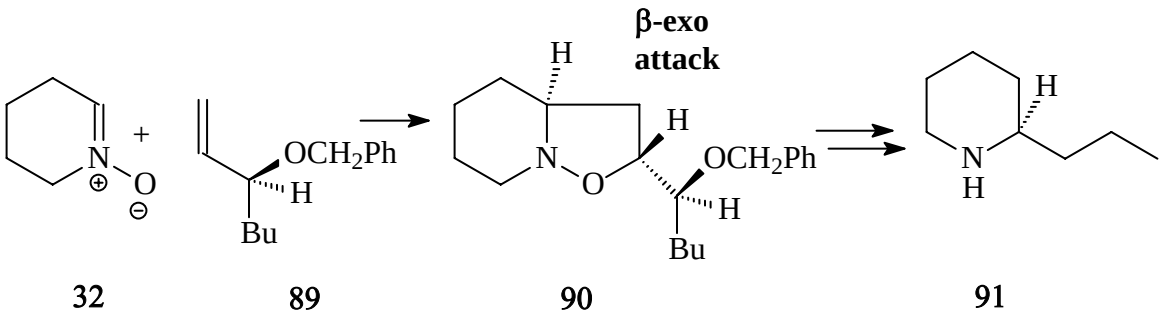
Scheme 23

Chiral allylic ether **86** afforded a 3:1 mixture of isoxazolidines from which the required major isomer **87** was converted to bicyclic amine, (+)-monomorine I **(88)** (Scheme 24).[41]



Scheme 24

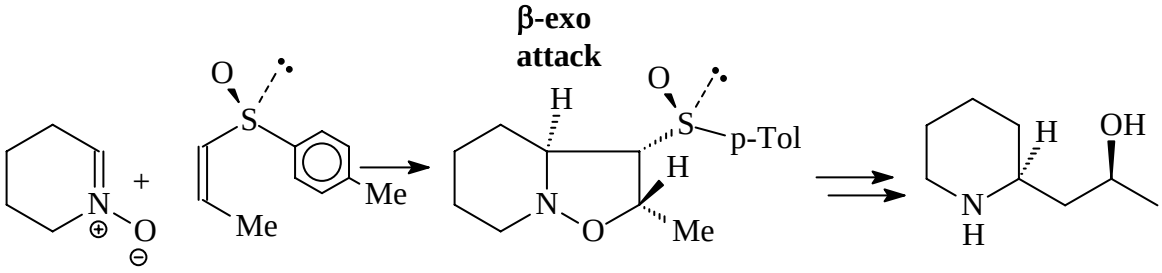
A similar reaction with the cyclic nitrone **32** afforded a mixture of cycloadducts (4:1 ratio), the major isomer **90** was coverted to (-)-conine **(91)** (Scheme 25)**.**[42]



32 89 90 91

Scheme 25

The chiral sulfoxide **92** on reaction with the cyclic nitrone **32** afforded **93** with only traces of a stereoisomer. The cycloadduct **93** was then converted to (+)-sedridine **(94)** (Scheme 26).[43]



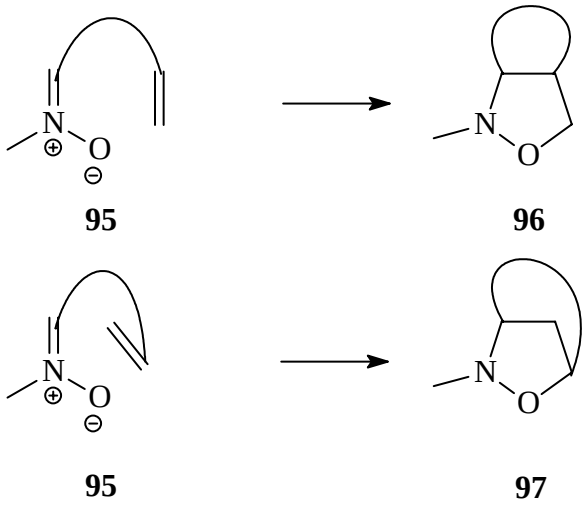
32 92 93 94

Scheme 26

2.3. Intramolecular nitrone-alkene 1,3-DC reactions

Due to the entropy factors, the activation barrier for intramolecular reactions is smaller in compare to the intermolecular reactions. The limited degree of spatial freedom in the transition state permits higher degree of regio- and stereo-selectivity in intramolecular reactions. The intramolecular nitrone-alkene reactions can be divided into

two types. The alkene part may be linked to the carbon atom or to the nitrogen atom of the nitrone. The majority of the reported reactions are those in which the alkene part is linked to the carbon atom of the nitrone. This type of linking can lead to two regioisomers **96** and **97** (Scheme 27). The most frequently observed product is the bicyclic compound **97**. In most cases the *exo* isomer is favored for sterical reasons.



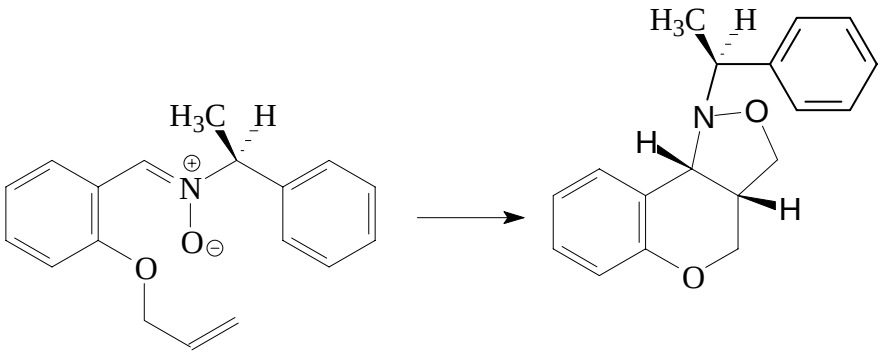
95 **96**

95 **97**

Scheme 27

2.3.1. Intramolecular 1,3-DC reactions of nitrone-alkene having chiral substituent located on the nitrogen terminal of the nitrone

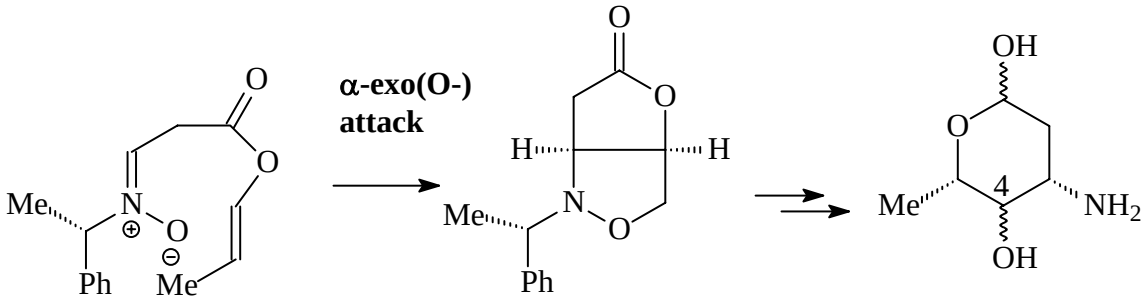
An intramolecular nitrone cycloaddition strategy was employed for the synthesis of enantiopure *(R)*- and *(S)*-3-hydroxymethylchromanes starting from allyl ethers of 2-hydroxybenzaldehydes, and *(R)-N*-(α-phenylethyl) as chiral auxiliary attached to the nitrone (Scheme 28).[44]



98 **99**

Scheme 28

Nitrone **100** underwent cycloaddition at 140°C to afford **101** (together with a stereoisomer) from which the alkaloids L-daunosamine and L-acosamine **(102)** were prepared (Scheme 29).[45]



100 **101**

102

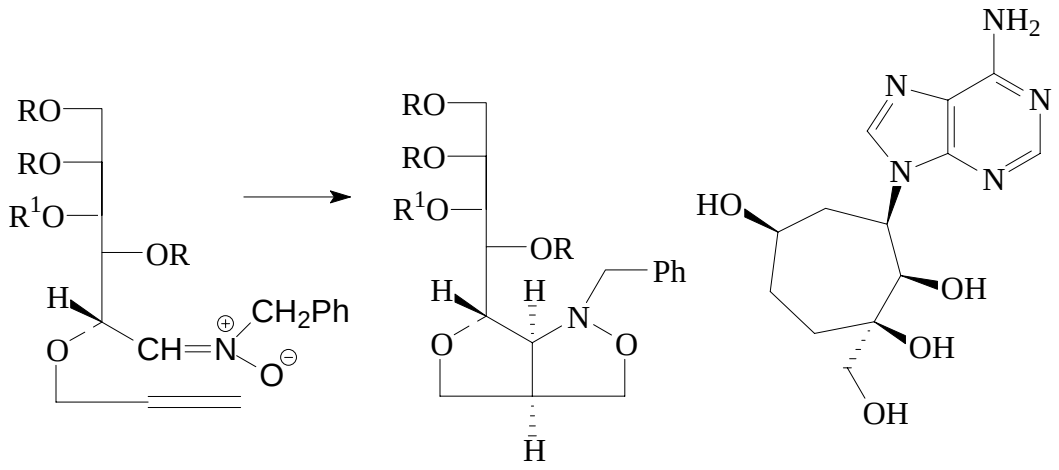
L-daunosamine 4α-OH

L-acosamine 4β–OH

Scheme 29

2.3.2. Intramolecular 1,3-DC reactions of nitrone-alkene having chiral substituent located on the carbon terminal of the nitrone

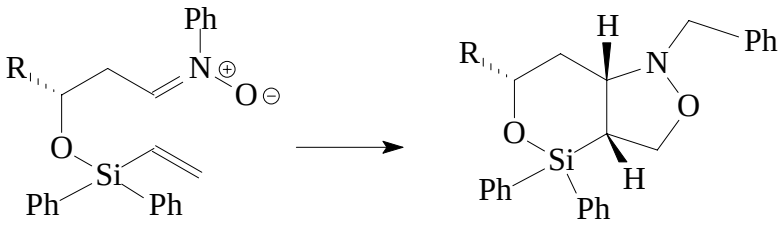
The intramolecular nitrone cycloaddition of 2-O-allylglucose derivatives **103** afforded optically pure tetrahydrofuranoisoxazolines **(104)**.[46] Also, intramolecular nitrone cycloaddition was applied to enose-nitrones derived from carbohydrates to synthesize chiral aminocarbocycles and carbocyclic nucleosides **(105)** (Scheme 30).[47]



103 **104** **105**

Scheme 30

Isoxazolidine derivatives have been synthesized through intramolecular cycloaddition reactions employing chiral nitrone **106**.[48,49] Scheme 31 shows an intramolecular cycloaddition of chiral nitrone **106** to a vinyl group tethered by a silicon atom. The resulting isoxazolidines **107** constitute direct precursors for stereodefined amino polyols. This approach is featured with high regioselectivity and diastereoselectivity.[48]



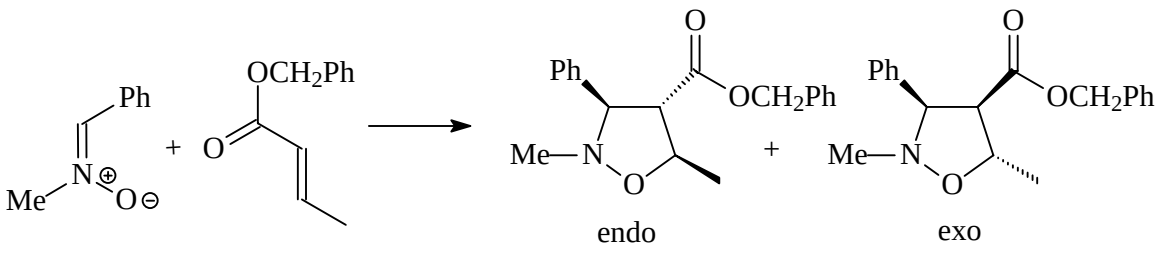
106 **107**

Scheme 31

2.4. Metal-catalyzed 1,3-DC reactions

2.4.1 Lewis Acid Catalyzed Nitrone Cycloadditions

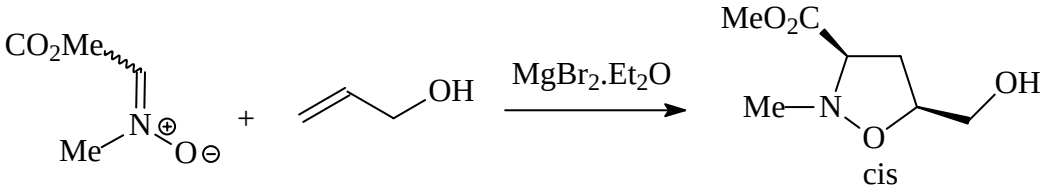
Contrary to the broad application of catalysts in asymmetric Diels-Alder reactions, the use of metal catalysts in nitrone cycloaddition reactions remained an unexplored area until recently. Kanemasa did important pioneering work in this field although he used racemic substrates. The addition reaction of **108** with **109** gave adducts **110** and **111** with an *endo*:*exo* ratio of 40:60 in the absence of catalyst (Scheme 32). In the presence of $ZnCl_2$ the *endo* isomer is formed predominantly. Reaction carried out in the presence of 1 equivalent of $Ti(O^iPr)_2Cl_2$, however, afforded the *endo* isomer as the sole product.[50] The presence of catalysts accelerates the rate of reactions trem*endo*usly.



108 **109** **110** **111**

Scheme 32

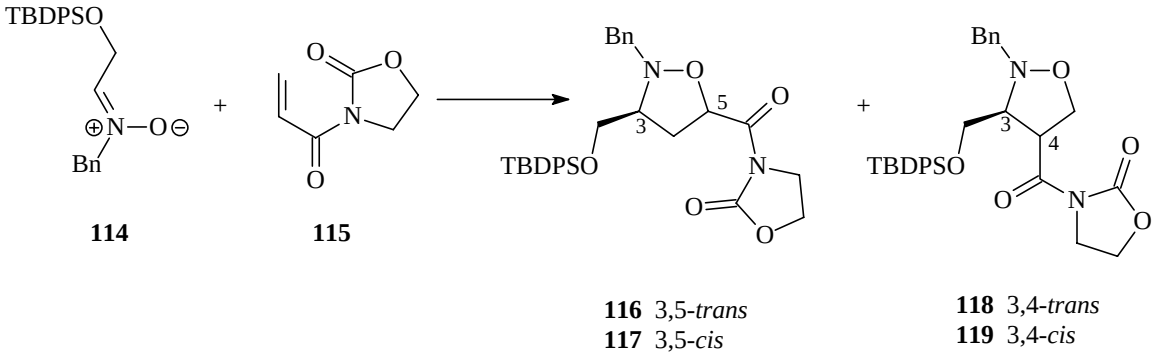
In extension of this work, Kanemasa et. al.[51,52] studied the reaction of allylic alcohols with nitrones in the presence of Mg(II) salts, $ZnBr_2$, $TiCl_2(O^iPr)_2$, or $BF_3.Et_2O$. The reaction of the nitrone **112** with allyl alcohol afforded the *cis* and *trans* isomers in a ratio of 44:56. In the presence of 1 equivalent $MgBr_2.Et_2O$, the *cis* isomer **113** is obtained as the sole product (Scheme 33).



112 **113**

Scheme 33

Recently, Fisera et.al [53,54] has reported the first example of the reversal of regioselectivity of a 1,3 DC caused by a Lewis acid in the case of chiral nitrones. In the absence of Lewis acid, nitrone **114** reacts with alkene **115** to give only **116** and **117** adducts in a ratio 75 : 25, while reaction in the presence of 1.1 equivalent $Ti(O^iPr)_2Cl_2$ gives **118** and **119** as the product in a ratio 77 : 23.



114 **115**

116 3,5-*trans*
117 3,5-*cis*

118 3,4-*trans*
119 3,4-*cis*

Scheme 34

2.4.2 Chiral Lewis Acid Catalyzed Nitrone Cycloadditions

Among 1,3-dipolar cycloaddition reactions, nitrone cycloadditions have been most widely studied from the standpoint of enantioselectivity. After great leading contributions from Jørgensen's group[55-62,69-72] as well as other groups including Furukawa[63,64], Kobayashi[65], Kanemasa[66], Scheeren[67,68], and others[73,74], this field has been developed to a high level of diastereoselectivity, enantioselectivity, and catalytic efficiency. All these reactions have been demonstrated successfully by use of dipolarophiles having chelating auxiliaries.

The catalytic enantioselective 1,3-dipolar cycloaddition reaction of nitrones can be divided into two major parts :

(i) <u>the normal electron-demand reactions</u>

The relative frontier molecular orbital (FMO) energies of the substrates of the 1,3-dipolar cycloaddition reaction are important for catalytic control of the reaction. In order to be able to control the stereochemistry of the reaction with a sub-stoichiometric amount

of a ligand–metal catalyst, it is desirable that large reaction rate accelerations are obtained to assure that the reaction only takes place in the sphere of the metal and the chiral ligand. The strategy that was applied for the catalytic enhancement of the reaction rate has therefore been to alter the relative energies of the FMOs of one of the substrates using chiral Lewis acids. This principle of activation can be applied to the 1,3-dipolar cycloaddition of nitrones in two different ways. The normal electron-demand involves the reaction of a nitrone with an electron-deficient alkene such as an α,β-unsaturated carbonyl compound. This reaction is primarily controlled by the interaction between $HOMO_{nitrone}$–$LUMO_{alkene}$ (Fig. 1). By the application of a Lewis acid (LA) catalyst which acts as an electron acceptor, the LUMO energy of the alkene is lowered by coordination of the α,β-unsaturated carbonyl to the Lewis acid. As a result of the decreased energy gap between the interacting FMO's, a rate acceleration of the reaction is achieved.[75] Examples of this type of catalyst are titanium, magnesium, palladium, lanthanide, and nickel catalysts.

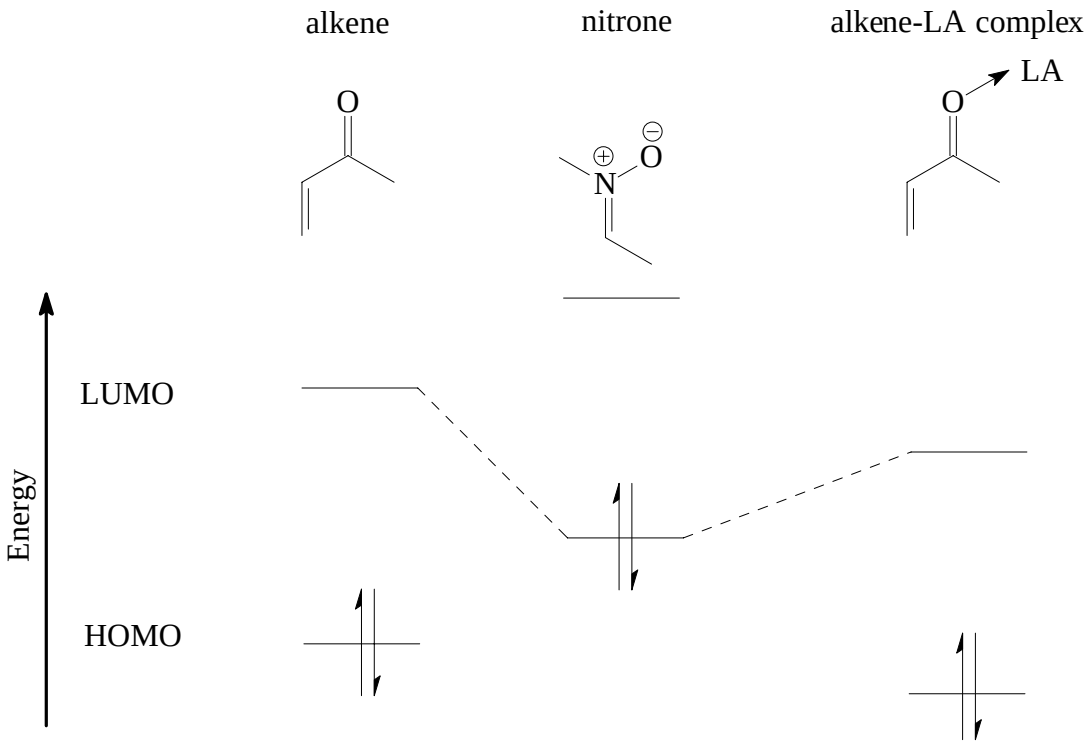
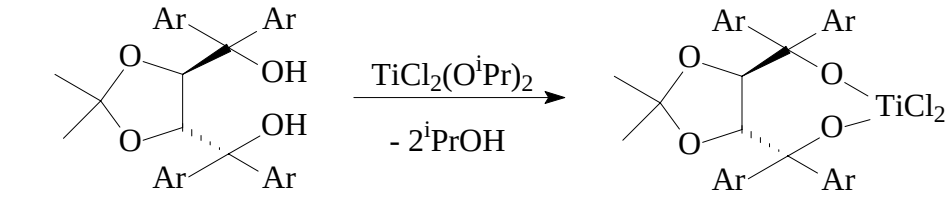
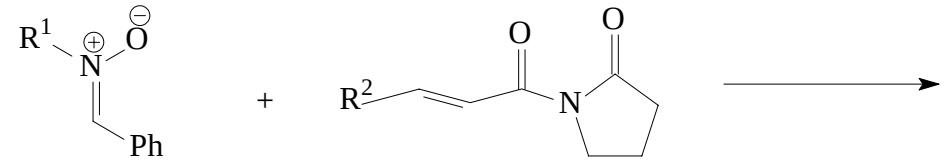


Figure 1 The catalytic alteration of the alkene FMO's in the normal electron demand 1,3-dipolar cycloaddition reaction.

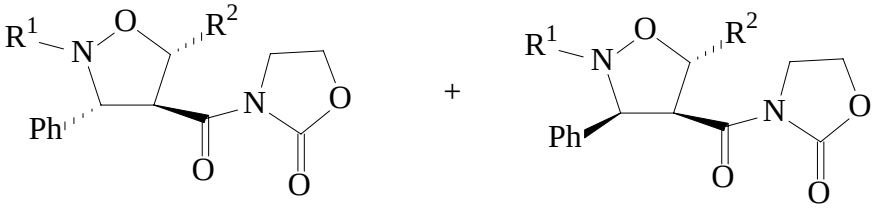
Several titanium(IV) complexes are efficient and reliable Lewis acid catalysts and have been applied to numerous reactions, especially in combination with the TADDOL (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol) (**120**) ligands. When 10 mol % of the catalyst **121** was applied in the reaction depicted in Scheme 35 the reaction proceeded to give a yield of up to 94%. The reaction led primarily to *exo*-**124** and in the best case an *endo*:*exo* ratio of 10:90 was obtained.[76]



120 **121**



122 **123**

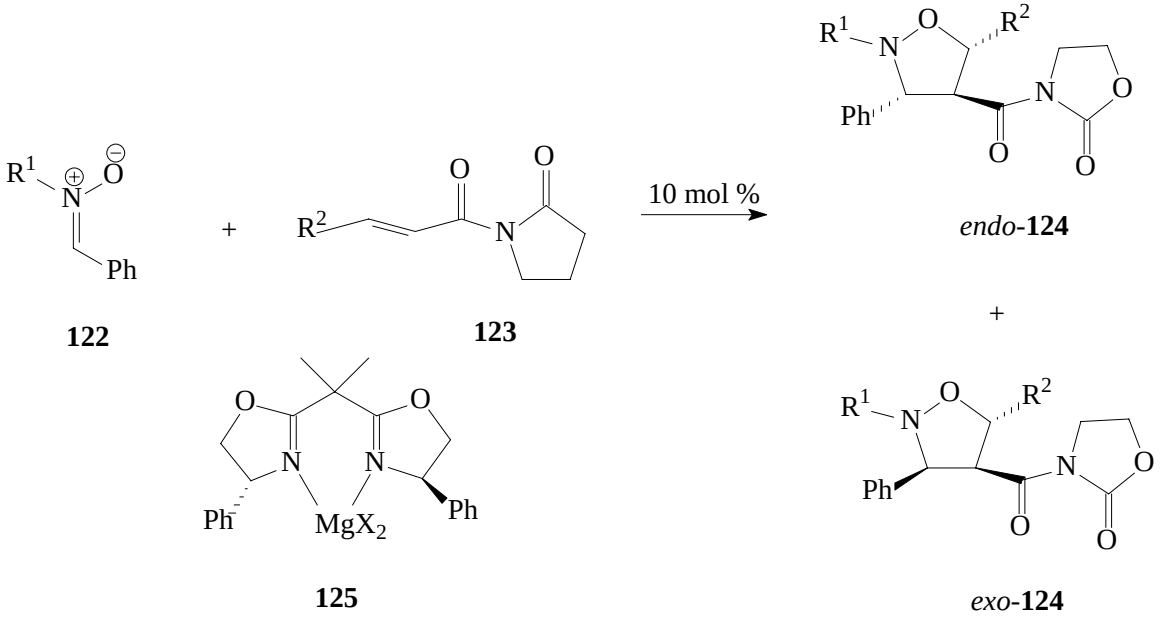


β-endo(CO_2R)-**124** *a-exo*(CO_2R)-**124**

Scheme 35

In the works applying chiral magnesium catalysts, chiral bisoxazolines (BOX) were applied as the ligand for magnesium. The MgX_2–Ph-BOX catalyst **125** (X = I),

proved to be a useful catalyst for the 1,3-dipolar cycloaddition between **122** and **123** when it was activated by the addition of I_2 (Scheme 36). Furthermore, the reaction had to be performed in the presence of molecular sieves (MS) 4 Å. In the presence of 10 mol% of **125** (X = I), the reaction proceeded with good to high *endo*-selectivity and the *endo*-isomer was obtained in an ee of up to 82%.[62]

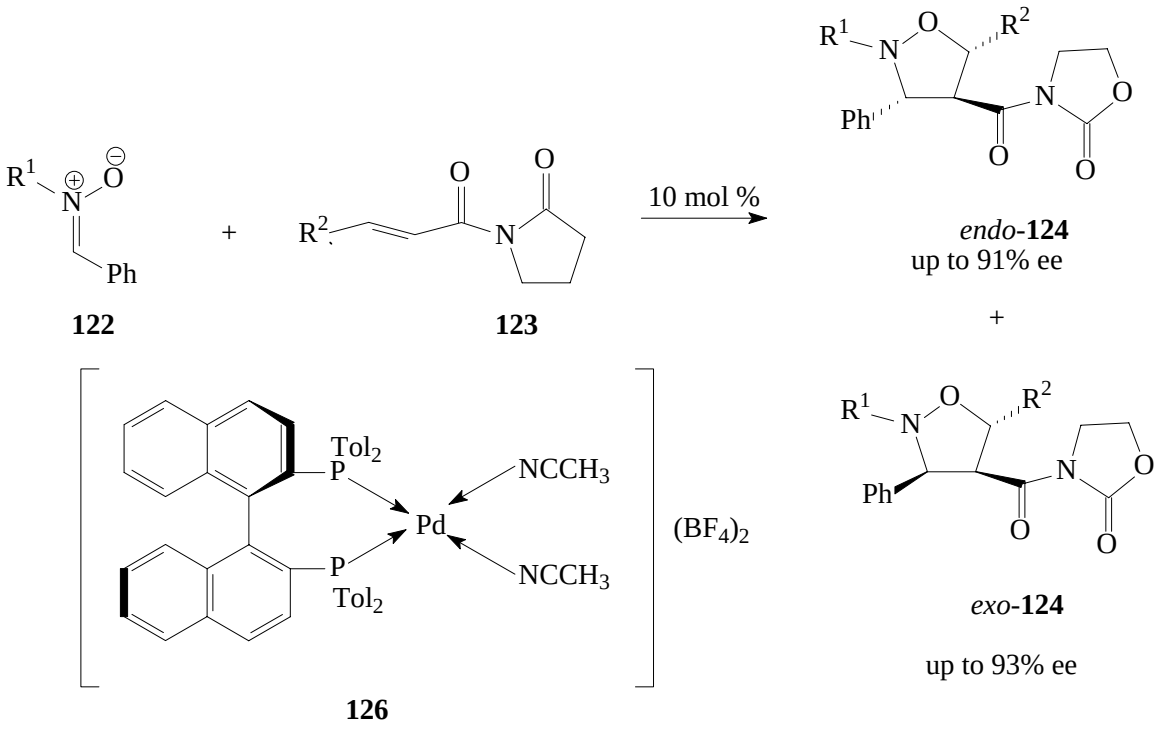


122 **123** **125**

Scheme 36

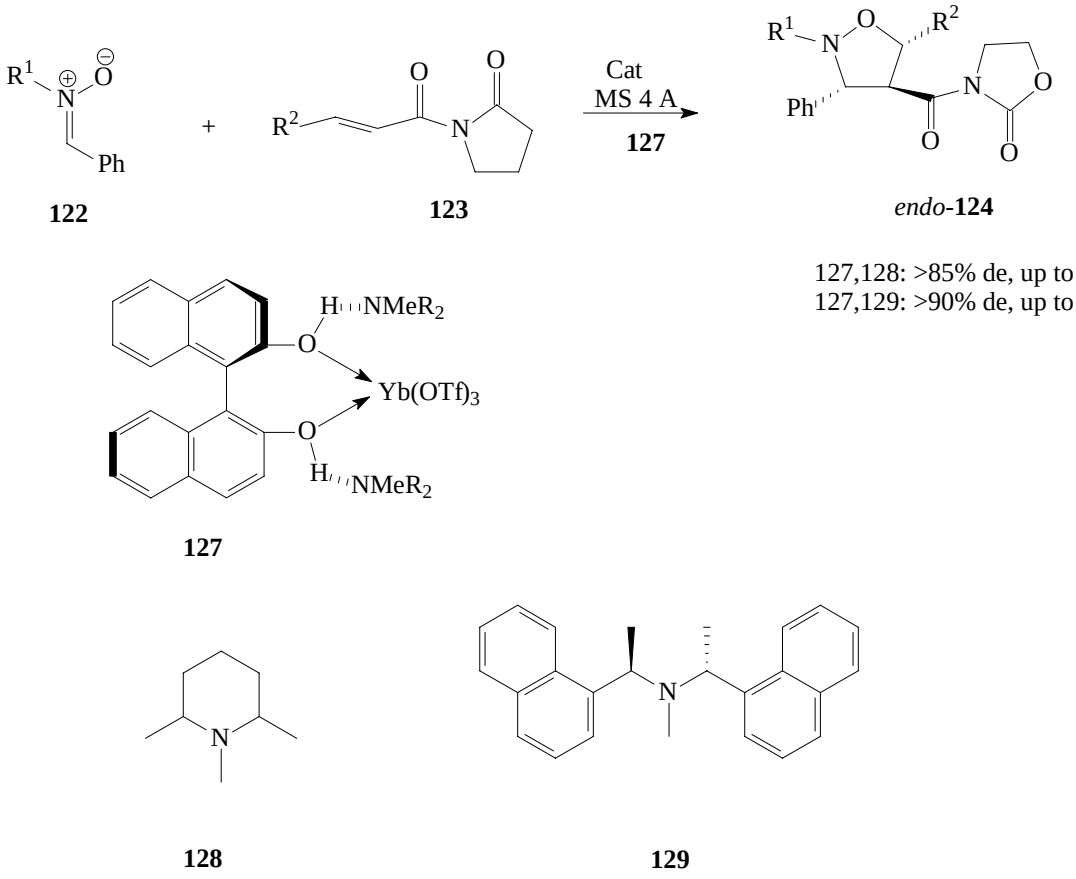
Furukawa *et al*. succeeded in applying the relatively soft d^{10} palladium as the catalyst for the 1,3-dipolar cycloaddition reaction between **122** and **123** (Scheme 37). They applied the dicationic Pd–BINAP **126** as the catalyst, and whereas this type of catalytic reaction is often carried out at room temperature, the reactions catalyzed by **126** required heating at 40°C in order to proceed. In most cases, mixtures of *endo*-**124** and

exo-**124** were obtained, however, high enantioselectives of up to 93% ee were obtained for reactions of some derivatives of **122**.[63,64]



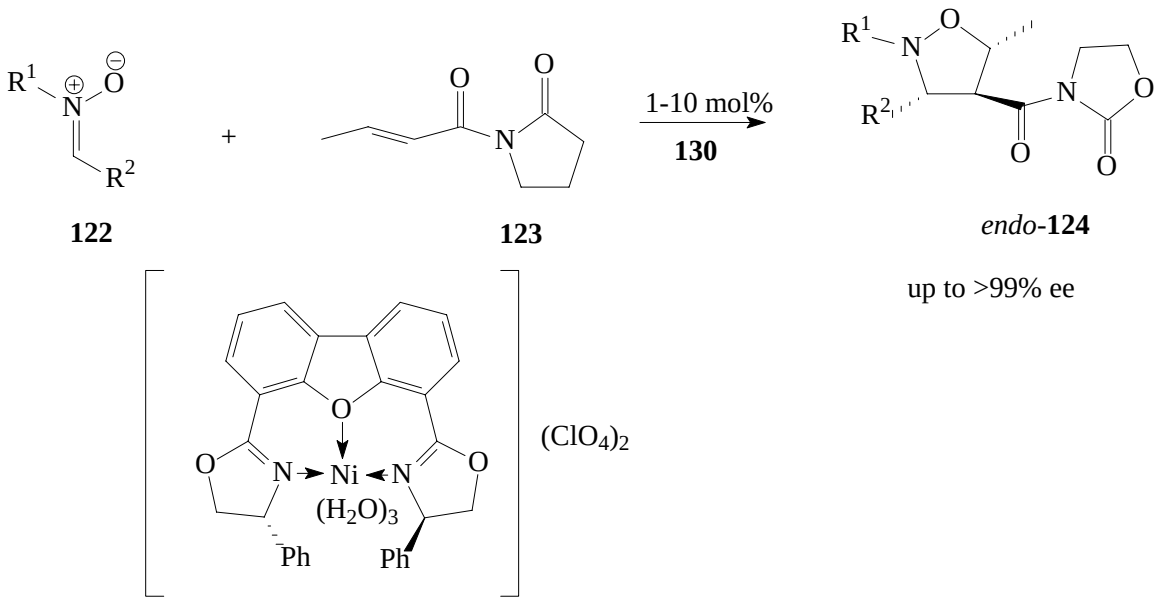
Scheme 37

Kobayashi *et al.* described a 1,3-dipolar cycloaddition between nitrone **122** and **123** catalysed by 20 mol % of the $Yb(OTf)_3$–BINOL complex **127** in the presence of the achiral tertiary amine **128 (**Scheme 38). High *endo*-selectivities were observed, and for one derivative the product *endo*-**124** was obtained with 78% ee. For the reactions of some derivatives of **122** and **123**, *endo*-**124** was obtained as a single diastereomer and with up to 96% ee. Further investigation in this field led to the finding that the absolute stereoselectivity of the reaction was reversed when the reaction was performed in the absence of MS 4 Å.[65]



Scheme 38

The reaction between different nitrones **122** and crotonoyloxazolidinone **123** proceeded in the presence of 1–10 mol% of the dicationic nickel complex **130** as the catalyst, in most cases, with very high *endo*-selectivities, and in several cases > 99% ee of the *endo* products **124** was obtained (Scheme 39).[66]



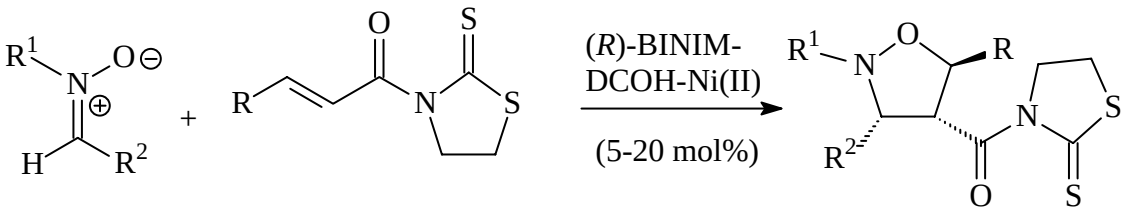
122 **123** *endo*-**124**

up to >99% ee

130

Scheme 39

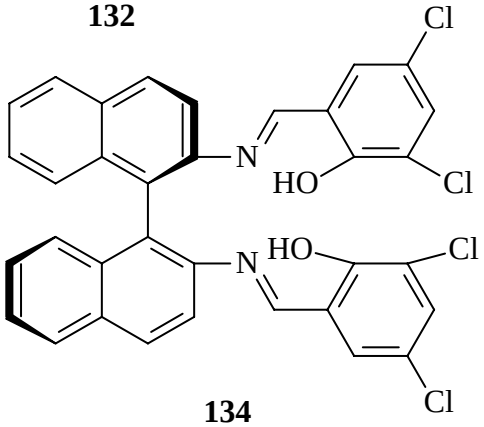
On the other hand, Suga[77] has reported a significant level of *exo*-selectivity ((*exo*: *endo*) >99:1 to 86:14) and enantioselectivity (95-82% ee) in the 1,3-dipolar cycloadditions of a number of nitrones **131** with 3-(2-alkenoyl)-2-thiazolidinethiones **132**, using the chiral binaphthyldiimine-Ni(II) complex (5-20 mol %) in the presence of 4 Å molecular sieves, as a chiral Lewis acid catalyst.



R^1 = Ar, Bn, Me
R^2 = Ar, Et

R = Me, Et, *n*-Pr, Ph

131 **132** **133**



(*R)*-BINIM-DCOH

134

Scheme 40

(ii) <u>the inverse electron-demand reactions</u>

In this approach, the nitrone is activated for addition to an electron-rich alkene such as, for example, a vinyl ether (Fig. 2). In this scenario, the FMOs of alkene have higher energies than the FMOs of nitrone and the dominating interaction in the reaction will be $LUMO_{nitrone}$–$HOMO_{alkene}$. The nitrone can coordinate to the Lewis acid, leading to a decrease of the $LUMO_{nitrone}$ energy. The decreased energy gap between the two FMO's responsible for the dominating interaction leads to an enhanced rate of the 1,3-dipolar cycloaddition reaction of nitrones. Examples of this type of catalyst are boron, aluminium, and copper catalysts.

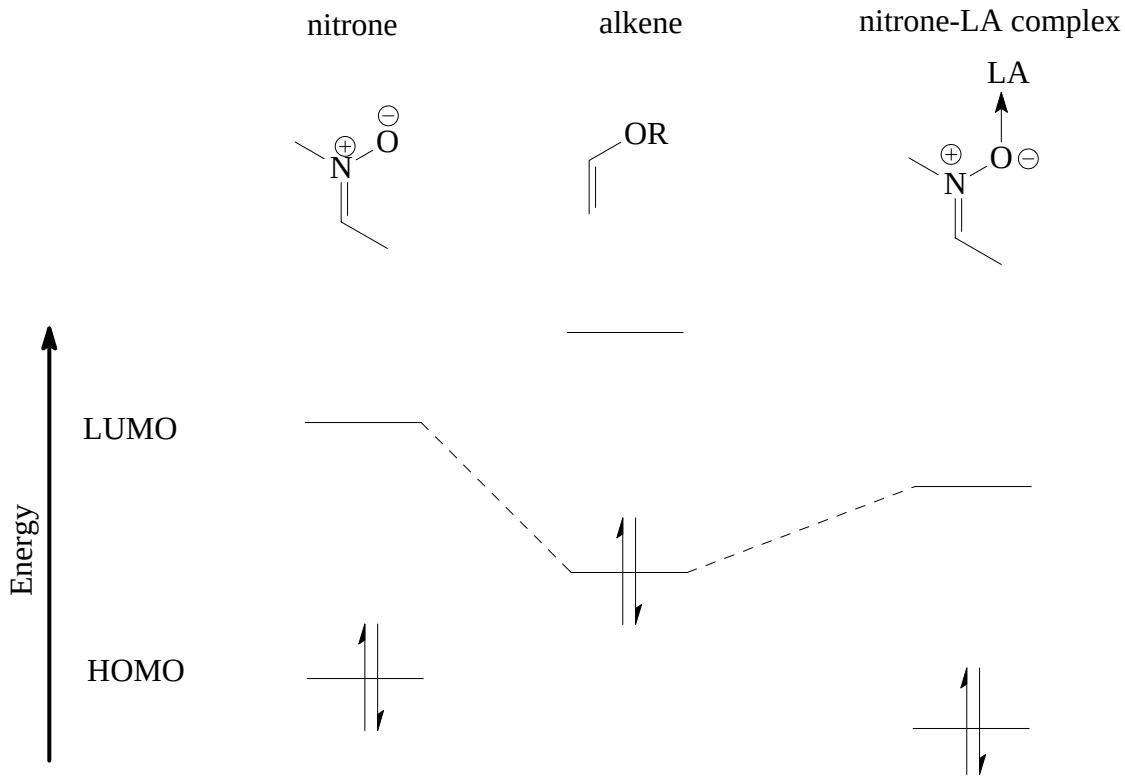
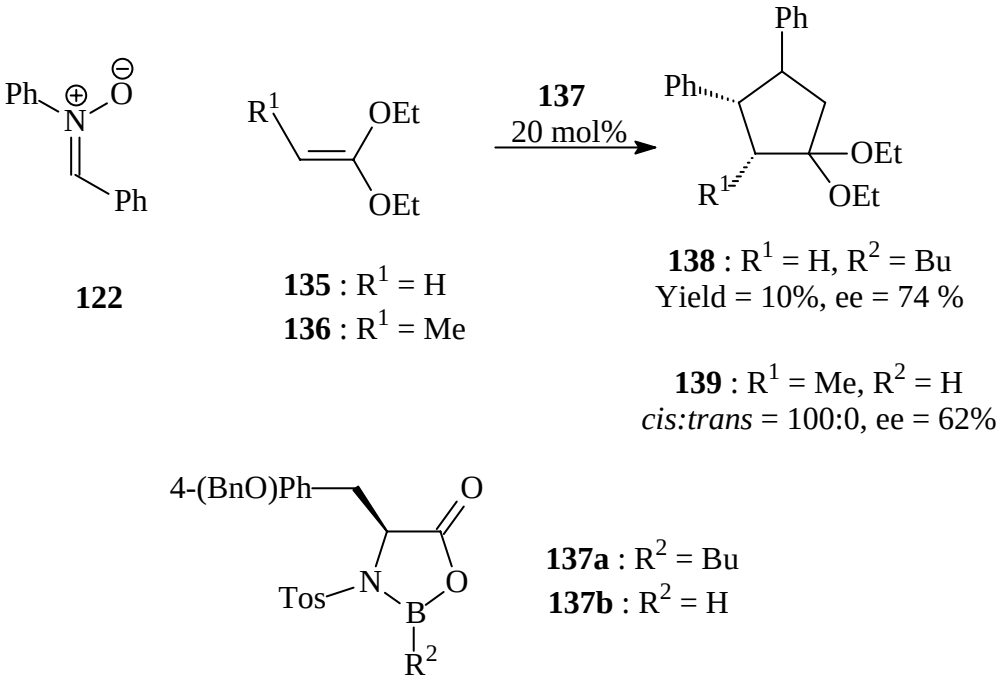


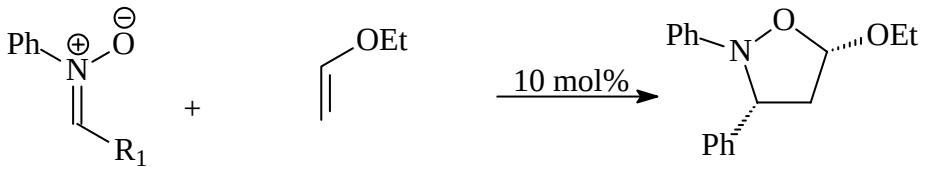
Figure 2. The catalytic alteration of the nitrone FMO's in the inverse electron demand 1,3-dipolar cycloaddition reaction.

The reactions of **122** with **135** and **136** were catalyzed by 20 mol % of oxazaborolidinones such as **137a**,**b**. Fair enantioselectivities were induced and **138** was obtained with an optical purity of 74% ee, however, in a low yield. The reaction involving **136** gave the *C*-3,*C*-4-*cis*-isomer **139** as the only diastereomer of the product with 62% ee[78] (Scheme 41).



Scheme 41

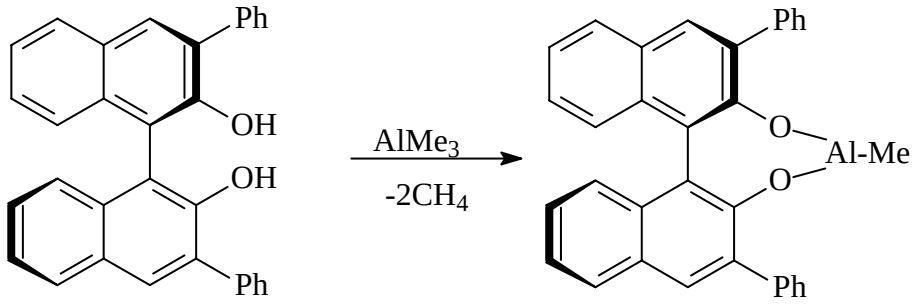
The reaction between a series of nitrones **122** as depicted in Scheme 42 using 20 mol% AlMe–BINOL catalyst **141**, proceeded to give the corresponding product **139** with excellent *exo*-selectivities and with enantioselectivities of 88–97% ee.[69]



a : R^1 = Ph
b : R^1 = *p*-tolyl
c : R^1 = *p*-ClPh
d : R^1 = *p*-MeOPh

exo
ee = 88-97%

122 **138** **139**

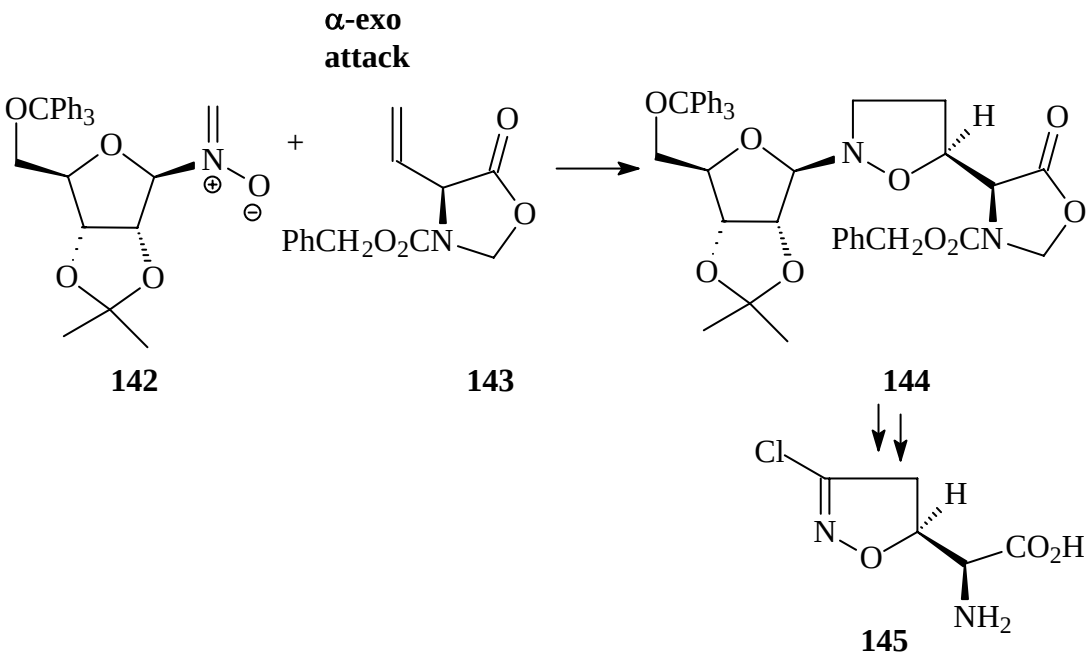


140 **141**

Scheme 42

2.5. Double Asymmetric induction in 1,3-DC reactions

Reaction between nitrone **142** and the protected vinylglycine derivative **143** afforded high yield of isoxazolidine with high levels of diastereoselectivity (80%, 19:1 isomeric ratio). The cycloadduct **144** was transformed to antimetabolite antibiotic Acivin (AT-125) (**145**).[79]


α-exo
attack
OCPh3
O
N
O
O
O
+
O
O
PhCH2O2CN
OCPh3
O
N
H
O
O
O
PhCH2O2CN
O
O
142
143
144
Cl
H
N
O
CO2H
NH2
145

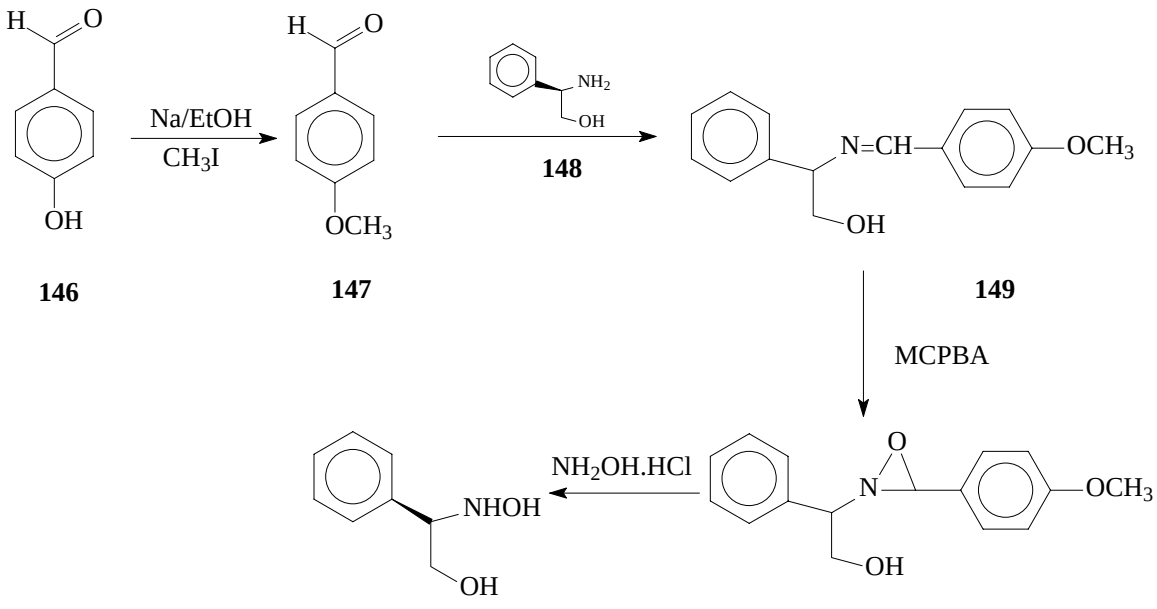
Scheme 43

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Preparation of chiral nitrone 7 and its 1,3-DC reactions with monosubstituted alkenes

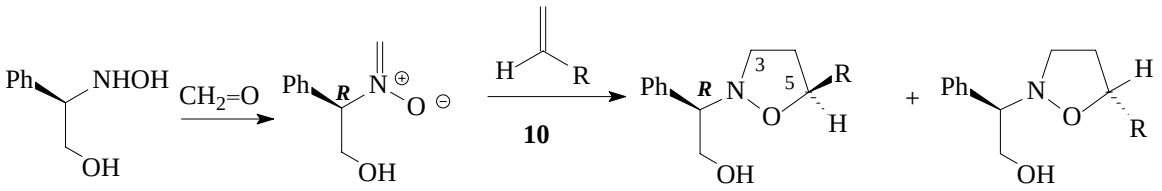
Chiral nitrone **7** used in the present study was prepared by condensation of chiral hydroxylamine **151** with formaldehyde. The chiral hydroxylamine was prepared according to the literature procedures[80,81] as shown in the Scheme 44.



146 **147** **148** **149** **150** **151**

Scheme 44

Reaction of anisaldehyde **147** with α-phenyl glycinol **148** gave the imine **149** which was then converted into isoxaziridine **150** by *meta*-chloroperbenzoic acid (MCPBA) and then into hydroxylamine **151** in overall 80 % yield.



151 **7** **13** **14**

a, R = Ph
b, R = CHO
c, R = CO_2Me
d, R = $CO_2{}^tBu$
e, R = CH_2OH

Scheme 45

Table 1.
Regio- and stereo- chemistry of the cycloaddition of the nitrone **7** with monosubstituted alkenes

Alkene **10**	Temp (°C)	Time (h)	Solvent	% composition of adducts **13**	**14**	Isolated yields (%)
a	0	144	$CHCl_3$	76	24	65
	25	72	$CHCl_3$	76	24	75
	50	6	$CHCl_3$	73	27	90
b	65	6	$CHCl_3$	44	56	65
c	0	144	$CHCl_3$	44	56	64
	25	72	$CHCl_3$	48	52	74
	50	6	$CHCl_3$	46	54	86
d	65	6	$CHCl_3$	56	44	85
e	85	6	Toluene	62	38	83

Initially, we choose to investigate the addition of the nitrone **7** onto several monosubstituted alkenes **10** (Scheme 45). All reactions were carried out under kinetically controlled conditions. Regio- and stereo-chemical details of these reactions along with the reaction temperature, solvent, isolated yield, and composition of isomeric cycloadducts are given in Table 1.

Addition of nitrone **7** to styrene **10a** at 50°C gave a non separable mixture of **13a** and **14a** in a ratio of 73:27 as determined by integration of the C5(H) signals. Similar ratio was found for the reaction at 0° and 25°C.

Addition of nitrone **7** to acrolein **(10b)** gave a non separable mixture of isomers **13b** and **14b**. The regio- and stereo-chemical outcome of this addition reaction was confirmed by reducing the mixture of adducts by sodium borohydride into the corresponding alcohol **13e** and **14e** of known configurations (*vide infra*). The ratio was found to be 44:56.

The reaction of methyl acrylate **(10c)** with **7** at 50°C gave a separable mixture of isomers of **13c** and **14c** in a ratio of 46:54, respectively, as determined by the integration of several proton signals in ^{1}H NMR spectrum in $CDCl_3$ of the crude reaction mixture. Decrease of the reaction temperature to 0° or 25°C did not change the product ratio. The crystalline appearance of **14c** enabled us to do an X-ray analysis. The stereochemistry for **14c** was found to be an *endo* product as shown in ORTEP drawing below.

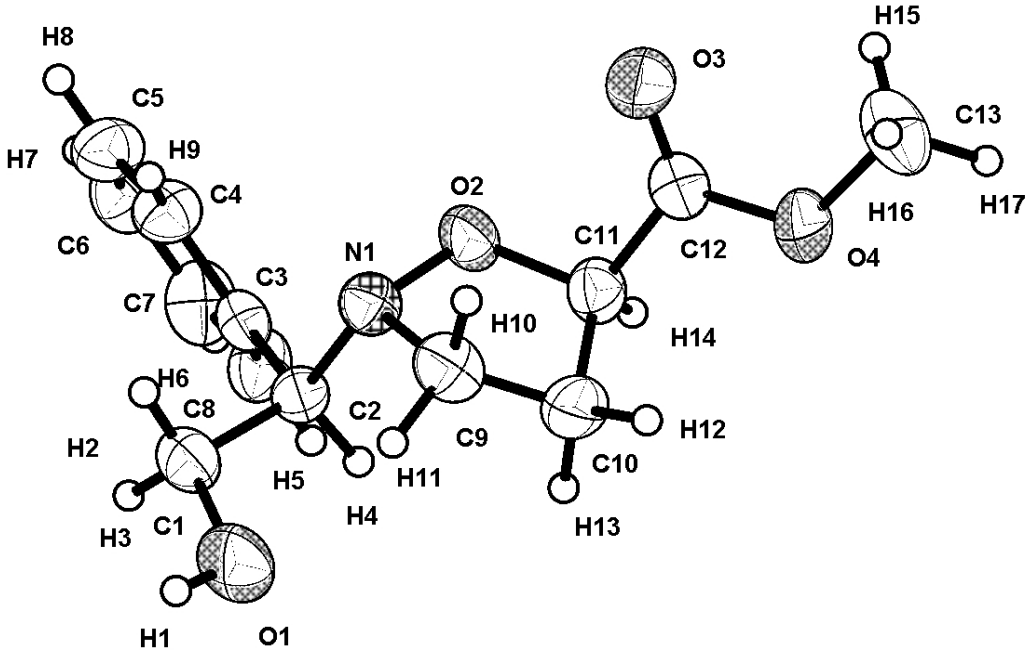
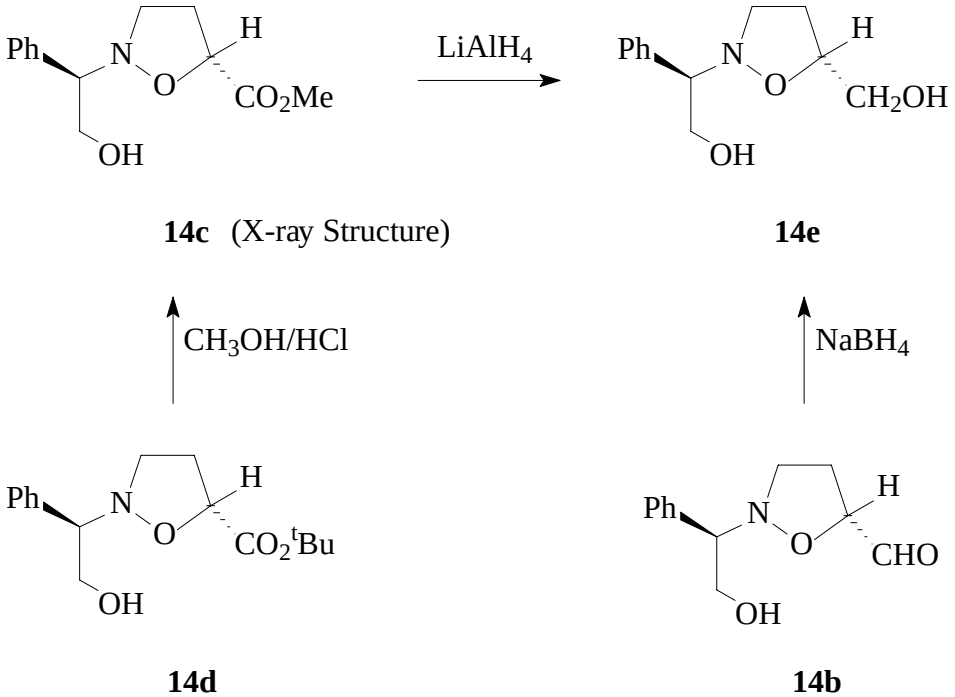


Figure 3 ORTEP drawing of **14c**

Reaction of tert-butyl acrylate **(10d)** with **7** gave **13d** and **14d** as a non separable mixture of isomers in a ratio of 56:44, respectively. The tert-butyl acrylate adducts were converted into the metyl acrylate adducts **13c** and **14c** by ester exchange with methanol (Scheme 46).

Addition reaction of allyl alcohol **(10e)** to nitrone **7** gave a non separable mixture of the cycloadducts **13e** and **14e**. Major and minor isomers were formed in a ratio of 62:38 as determined by integration of non overlapping proton signals at δ2.08 (1H, m), 2.31 (1H, m) for the major, and at δ2.14 (2H, m) for minor isomer.

The configurations of the cycloadducts were confirmed by chemical transformations as shown in Scheme 46. Since the structure of **14c** was confirmed by X-ray analysis, its conversion to allyl alcohol adduct **14e** (by reduction with $LiAlH_4$) paved the way to establish the configuration of acrolein adduct **14b.**



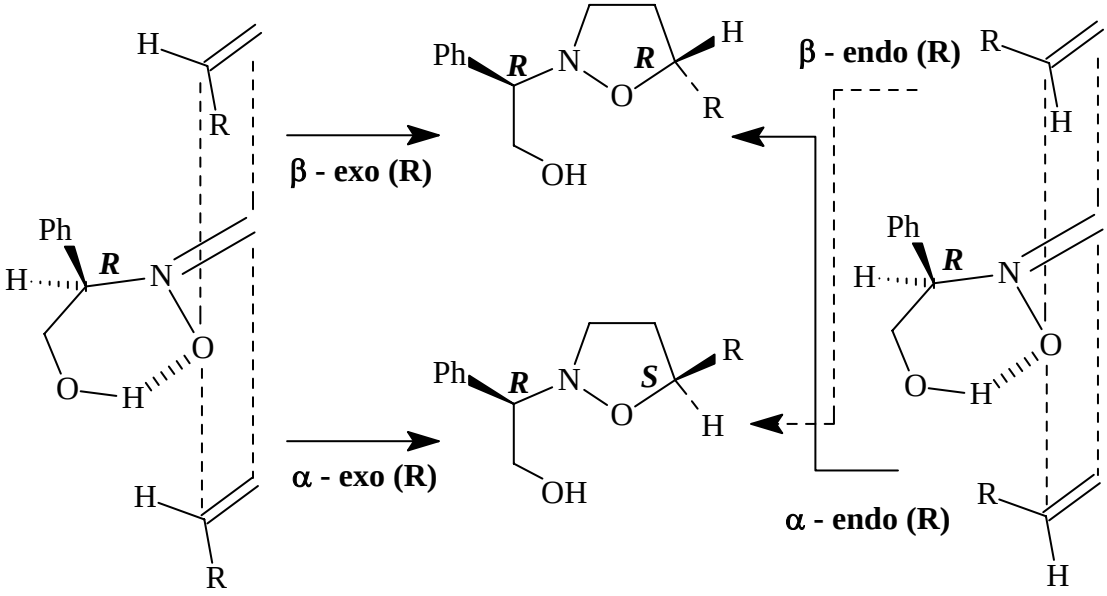
14c (X-ray Structure) **14e**

14d **14b**

Scheme 46

The nitrone **7** is expected to be internally H-bonded as shown in Scheme 47. This would place the phenyl group on the β-face of the nitrone while the H on the chiral carbon remains in the α-face. While both the 'α-*exo* (R) approach' (i.e. the approach of the alkene with *exo*-oriented R toward the α-face of the nitrone) and 'β-*endo* (R) approach' of the alkene would lead to the same diastereomer with '*RS*' configuration, the 'α-*endo* (R)' and 'β-*exo* (R)' approaches give the other diastereomer having '*RR*' configuration. The face and stereo-selectivity in the addition reaction of methylene nitrones, like **7**, can not be determined since, for instance, the formation of the '*RS*' diastereomer is the combined outcome of attacks of both faces of the nitrone. Likewise, the stereoselectivity (*exo*/*endo* ratio) cannot be determined since each diastereomer can be obtained by both the *exo* and *endo* mode of attack. This problem does not arise in the cases of C-substituted nitrones since their addition reactions would create three chiral centers and as such each of the approaches would generate different diastereomer, thus allowing the determination of face and stereo-selectivity. For the current nitrone **7**, it can be presumed that the α-face of the nitrone will be preferably attacked, and the steric and secondary orbital interactions would then dictate the mode of approach (*exo* or *endo*). In line with this reasoning, the styrene cycloaddition resulted in the formation of the major adduct **13a** predominantly via 'α-*exo* (R) approach' whereby steric factor of the phenyl group in styrene overwhelms any possible secondary orbital interactions in an *endo* approach. The alkenes: acrolein and methyl acrylate, on the other hand favored 'α-*exo* (R) approach' with the formation of the diastereomer **14** in slight excess over **13** as a result of favorable secondary orbital

interactions by the carbonyl groups. Allyl alcohol and the sterically crowded t-butyl acrylate tilted slightly in favor of the formation of the adducts **13** via 'α-*exo* (R) approach'.

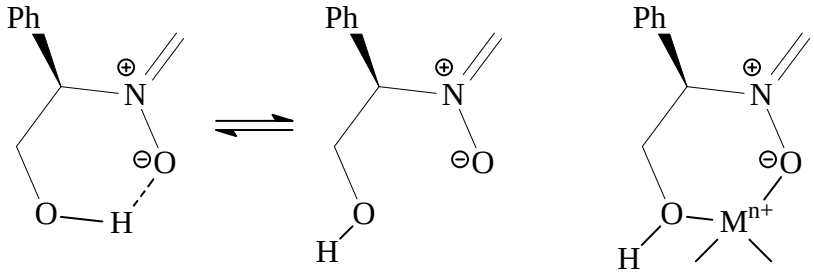


Scheme 47

3.1.1 Cycloaddition of nitrone 7 with monosubstituted alkene 10 in the presence of *Lewis* acids

Cycloaddition reaction of the chiral nitrone **7** with styrene (**10a**) and methyl acrylate (**10c**) were carried out in the presence of Lewis acid catalysts like $BF_3.OEt_2$, $Ti(O^iPr)_4$ and $MgBr_2$. The stereochemical analyses were given in Table 2. As evident from the Table the addition of styrene in the presence of one equivalent of $MgBr_2$ resulted in the increase of the ratio to 86:14 in favor of the isomer **13a** with *exo*-oriented phenyl group. The ratio in the absence of any catalyst was found to be 73:27 (*vide supra*). The results thus indicate that the nitrone takes a cyclic form by virtue of coordination with the metals (Scheme 48).

It is to be mentioned that the cyclic form of the H-bonded nitrone may not be stable enough since it can equilibrate to the non H-bonded acyclic form. The metal-chelated nitrone enjoys the stereochemical preferences inherent in a cyclic nitrone thereby preferring the α–*exo*-mode of attack by the styrene as observed in the cycloaddition of many cyclic nitrones.[8]



Scheme 48.

Table 2.
Regio- and stereo- chemistry of the cycloaddition of the nitrone **7** with monosubstituted alkenes in the presence of *Lewis* acids

Alkene **10**	Temp (°C)	Reaction Time (h)	Solvent	% composition of adducts **13**	% composition of adducts **14**	Isolated yields (%)	*Lewis* Acid
a	50	6	$CHCl_3$	73	27	90	None
	75	24	$CHCl_3$	79	21	75	$BF_3.OEt_2$
	65	24	CH_2Cl_2	86	14	92	$MgBr_2$
c	50	6	$CHCl_3$	46	54	86	None
	65	24	$CHCl_3$	38	62	85	$BF_3.OEt$
	65	6h	$CHCl_3$	62	38	83	$Ti(O^iPr)_4$

The result discussed above are in general agreement with the frontier orbital treatment of the nitrone 1,3-dipolar cycloadditions.[4,82-87] the case of monosubstituted alkenes both nitrone(HOMO)-alkene(LUMO) contributions does not offer any regiochemical preference since the nitrone HOMO has similar magnitude of orbital coefficients at both the nitrogen and carbon terminals. However the nitrone(LUMO)-alkene(HOMO) prefer the formation of 5-substituted regioisomers by uniting the larger terminal coefficient in the transition state. (Figure 4).[88, 89]

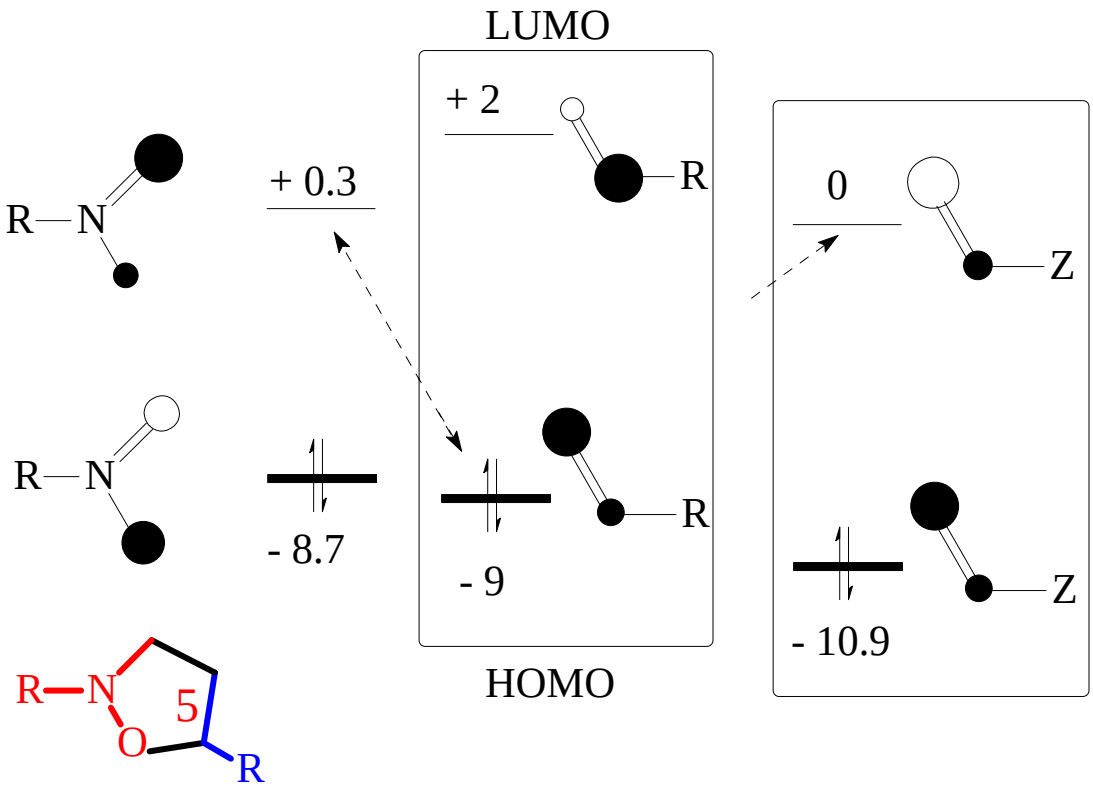
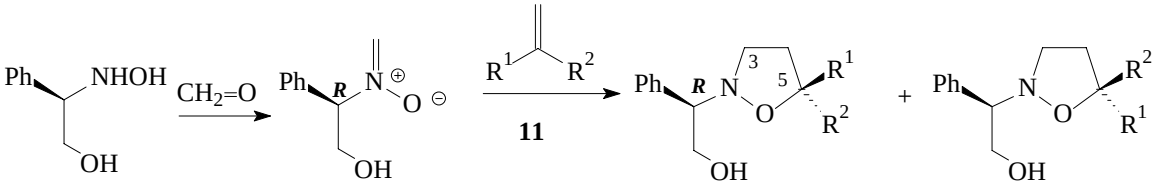


Figure 4. Qualitative Representation of Frontier Orbital Energies and Orbital coefficients of Nitrone and Monosubstituted Alkene

3.2 1,3-DC reaction of chiral nitrone 7 with 1,1-disubstituted alkenes (11)

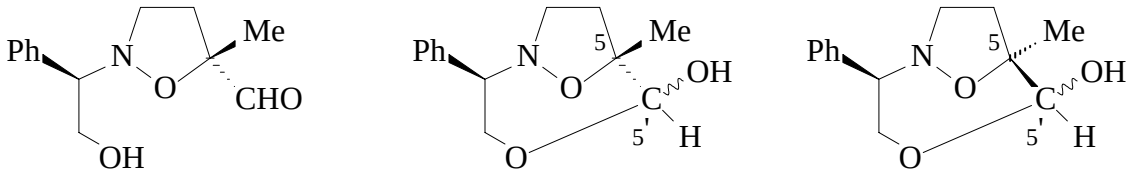


7 **15** **16**

a, R^1 = Me; R^2 = CHO
b, R^1 = Me; R^2 = CO_2Me
c, R^1 = Me; R^2 = $CO_2{}^tBu$
d, R^1 = Me; R^2 = CH_2OH
e, R^1 = Me; R^2 = $CH_2OSi^tBuMe_2$
f, R^1 = R^2 = CO_2Me

Scheme 49

Next, we pursued the cycloaddition of the nitrone **7** with a number of 1,1-disubstituted alkenes **11** (Scheme 49). The results of the stereochemical analysis are recorded in Table 3. The addition of methacrolein **11a** to nitrone **7** gave the hemiacetals **15a'** and **16a'** instead of the expected adducts **15a** and **16a** (in the aldehyde form**).**



15a **15a'** **16a'**

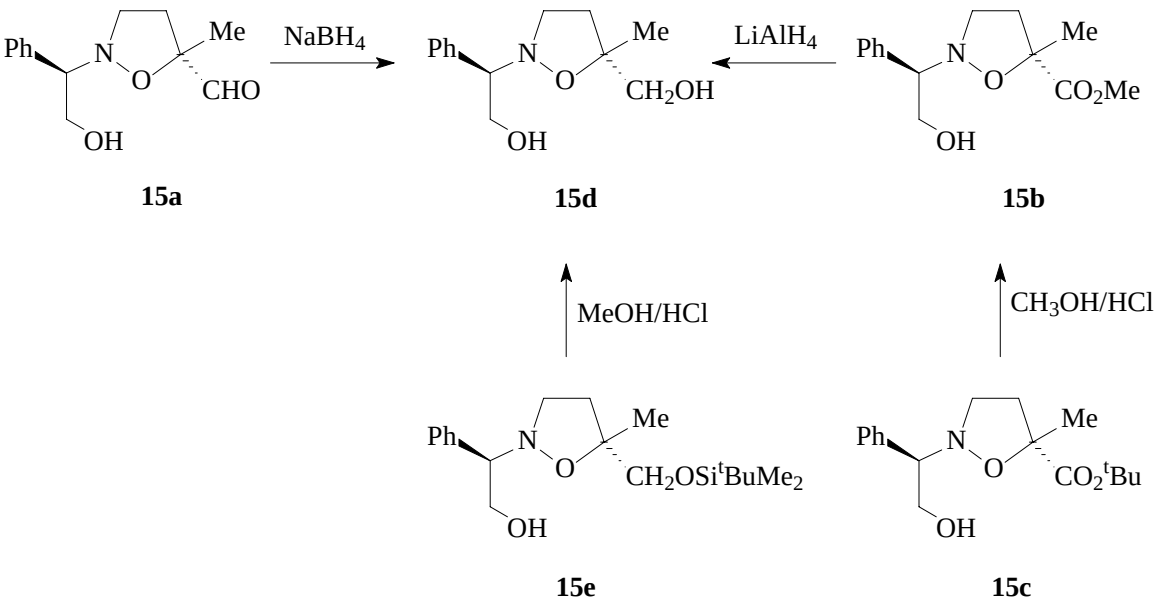
Scheme 50

Table 3.
Stereochemistry of cycloaddition of the nitrone **7** with 1,1-disubstituted alkenes **11**

Alkene **11**	Temp (°C)	Time (h)	Solvent	% composition of adducts		Isolated yields (%)
				15	**16**	
a	65	6	$CHCl_3$	66	34	93
b	50	6	$CHCl_3$	86	14	80
c	65	6	$CHCl_3$	87	13	85
d	90	6	Toluene	67	33	82
e	95	6	Toluene	60	40	74
f	50	6	$CHCl_3$	100		90

We were able to isolate one of the hemiacetals - presumably the **15a'** - in pure form. IR spectrum failed to reveal the presence of carbonyl group. The ^{1}H NMR spectrum revealed the presence of hemiacetal C(5')H at δ4.69 (1H, d, *J* 4.3 Hz), which on D_2O exchange collapsed into a singlet while the signal at δ3.06 (1H, d, *J* 4.3 Hz, OH) disappeared. The spectrum revealed the presence of a trace amount of aldehyde by displaying signal at δ9.62 ppm. It also revealed the presence of a minor hemiacetal **15a'** by displaying signal of the methyl proton as a singlet at 1.41 ppm. The ratio of the two hemiacetals was found to be 90:10, however, during D_2O exchange, the ratio was changed to 64:36. In the crude reaction mixture, the ratio of the two hemiacetals of **15a'** was also found to ~64:36. The stereochemistry of the adducts was correlated to the methallyl alcohol adducts **15d** and **16d** by $NaBH_4$ reduction of the crude cycloaddition products (Scheme 51) (*vide infra*). The ratio of the isomers **15a** and **16a** was determined to be 66:34, respectively. For the favorable secondary orbital interactions, the aldehyde group is assumed to have the *endo* orientation in **15a,** presumably formed *via* 'α-*endo* (CHO) approach' for the reasons as discussed in the previous section.

The cycloaddition of **7** with methyl methacrylate **11b** gave a separable mixture of **15b** and **16b** in a ratio 86:14 as determined by integration of several proton signals in ^{1}H NMR. The cycloaddition at 0 and 25°C gave the adduct **15b** and **16b** in a ratio of 90:10 and 87: 13, respectively. The stereochemistry of the adduct was correlated to the methallyl alcohol adducts **15d** and **16d** by lithium aluminium hydride reduction of the crude cycloaddition products (Scheme 51) (*vide infra*).



Scheme 51

Addition of nitrone **7** with *tert*-butyl metacrylate **11c** gave a non separable mixture of cycloadducts **15c** and **16c** in a ratio of 87:13 as determined by NMR spectrum of the crude as well as the purified mixture. C(5) methyl protons appeared as singlets at δ1.49 (major) and 1.50 (minor) ppm while the t-butyl proton appeared at δ1.52 (major) and 1.53 (minor) ppm in a ratio of 87:13, respectively. The tert-butyl methacrylate adducts **15c** and **16c** were converted into the methyl methacrylate adducts **15b** and **16b** by ester exchange with methanol (Scheme 51).

Reaction of nitrone **7** with methalyl alcohol **11d** gave a nonseparable mixture of cycloadducts **15d** and **16d** in a ratio of 67:33. The addition of silylether alkene **11e** afforded cycloadducts **15e** and **16e** in a 60:40 ratio. The stereochemistry of the cycloadducts was correlated to the methallyl alcohol adducts by conversion of **15e** and **16e** using methanolic HCl into the corresponding alcohols **15d** and **16d**. Reaction of

nitrone **7** with dimethyl methylenemalonate **11f** gave the cycloadduct **15f** as the sole regiomer in an excellent yield.

The addition reaction of the chiral nitrone **7** onto 1,1-disubstituted alkenes **11** gave better face and stereo-selectivity than their monosubstituted counterparts **10** (*vide supra*) as a result of marked preference for the 'α-*endo* (-C=O) approach'. While in monosubstituted alkenes, the steric factor (H *vs.* R) and secondary orbital interactions operate in opposite directions for the stereoselection, the secondary orbital interaction is the dominant player in **11** since the steric differences between 'Me' and '–C=O' are very minimal. Significant preference for the *endo*-approach observed in the addition of even the ^{t}butyldimethylsilyl ether of methylallyl alcohol is probably due to the stabilizing interaction between the nitrogen atom of the nitrone LUMO with the oxygen lone pair of the alkene (Figure 4). Similar stabilizing interaction has been reported earlier.[8, 10, 91]

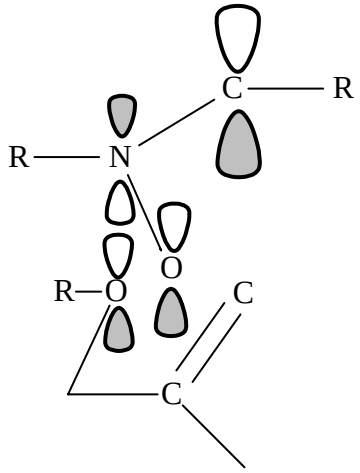
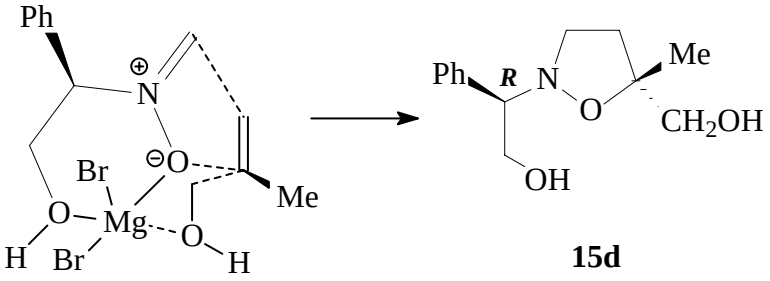


Figure 5. Stabilizing interaction between nitrogen in nitrone LUMO and oxygen lone pair of the alkene

3.2.1. 1,3-DC reaction of chiral nitrone 7 with 1,1-disubstituted alkenes (11) in the presence of *Lewis* acid

Cycloaddition reaction of the chiral nitrone **7** with methyl methacrylate (**11b**) and methylallyl alcohol (**11d**) were carried out in the presence of Lewis acid catalysts like $BF_3.OEt_2$, $MgBr_2$. The stereochemical analyses are given in Table 4. As evident from the Table the addition of methylallyl alcohol in the presence of one equivalent of $MgBr_2$ resulted in a dramatic increase of the ratio to 97:3 in favor of the isomer **15d** with *endo*-oriented hydroxyl group. The ratio in the absence of any catalyst was found to 67:33. The results thus indicate that the nitrone takes a cyclic form and the hydroxyl group of the alkene is complexed to the metal (Scheme 52). This forces the hydroxymethyl group of the alkene to assume *endo* orientation prior to cycloaddition reaction. Similar observation was made in cycloaddition reaction with Lewis acid catalyst.[92,93]



Scheme 52.

Table 4.
Stereochemistry of cycloaddition of the nitrone **7** with 1,1-disubstituted alkenes **11** in the presence of *Lewis* acids

Alkene **11**	Temp (°C)	Reaction Time (h)	Solvent	% composition of adducts **15**	% composition of adducts **16**	Isolated yields (%)	*Lewis* Acid
b	50	6	$CHCl_3$	86	14	80	None
	65	24	$CHCl_3$	86	14	84	BF_3.OEt
d	90	6	toluene	67	33	82	None
	65	24	CH_2Cl_2	97	3	95	$MgBr_2$

The result discussed above are in general agreement with the frontier orbital treatment of the nitrone 1,3-dipolar cycloadditions.[4,82-87] In the case of 1,1-disubstituted alkenes both nitrone(HOMO)-alkene(LUMO) contributions does not offer any regiochemical preference since the nitrone HOMO has similar magnitude of orbital coefficients at both the nitrogen and carbon terminals. However the nitrone(LUMO)-alkene(HOMO) prefer the formation of 5-substituted regioisomers by uniting the larger terminal coeffient in the transition state. (Figure 6).[88,89]

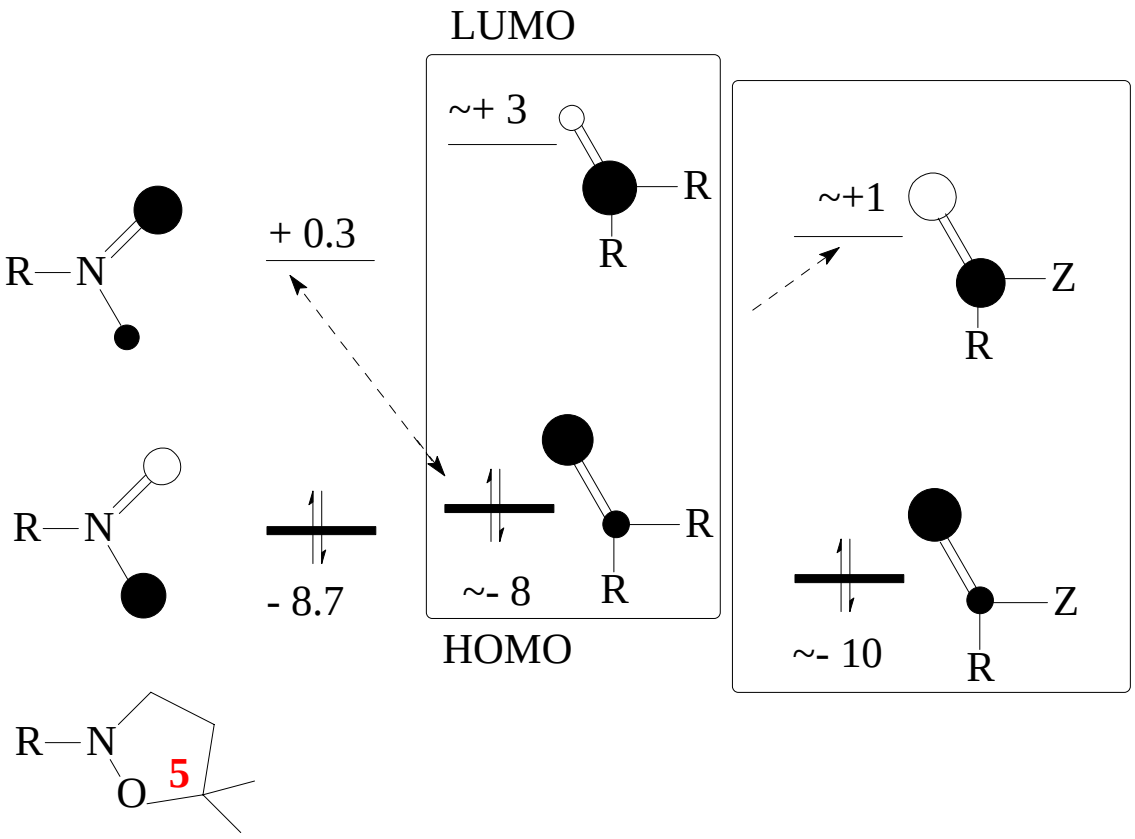
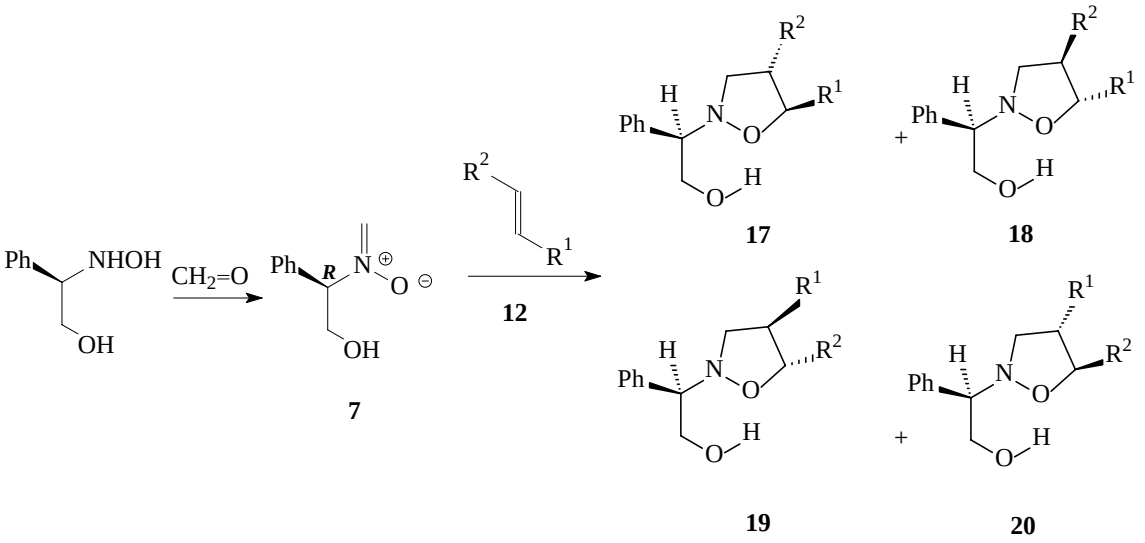


Figure 6. Frontier Orbital energies of nitrone and 1,1-disubstitited alkenes

3.3 1,3-DC reaction of chiral nitrone 7 with 1,2-disubstituted alkenes (12)

Next, we studied cycloaddition of nitrone **7** with several 1,2 disubstituted alkenes. The stereochemical analysis of these additions is summarized in Table 5. The nitrone **7** upon reaction with *trans*-methyl crotonate **12a** afforded adducts **17a-20a** in a ratio 57:9: 16:18, respectively. The regioisomeric ratio was thus found to be 66:34 in favor of the isomers **17a** and **18a**. The NMR spectrum in toluene-d_8 at 20°C was helpful in the determination of composition. In this solvent, the C(5)-methyl protons of **17a** and **18a**, and C(4)-methyl of **19a** and **20a** appeared at 1.13 (d, *J* 6.1), 1.16 (d, *J* 6.1), 0.83 (d, *J* 7.0), 0.78 (d, *J* 6.8), while the corresponding CO_2Me peak appeared as singlet at 3.25, 3.21, 3.32, 3.33 ppm, respectively. The downfield signals were attributed to the C(5)-Me protons of **17a** and **18a** because of their proximity to the electronegative ring oxygen, while the same reasoning was applied in assigning the downfield C(5)-CO_2Me singlets to the isomers **19a** and **20a**.



a, R^1 = Me; R^2 = CO_2Me
b, R^1 = Me; R^2 = $CO_2{}^tBu$
c, R^1 = Me; R^2 = CHO
d, R^1 = Me; R^2 = CH_2OH
e, R^1 = CH_2OH; R^2 = CO_2Me
f, R^1 = Ph; R^2 = CO_2Me
g, R^1 = Ph; R^2 = $CO_2{}^tBu$

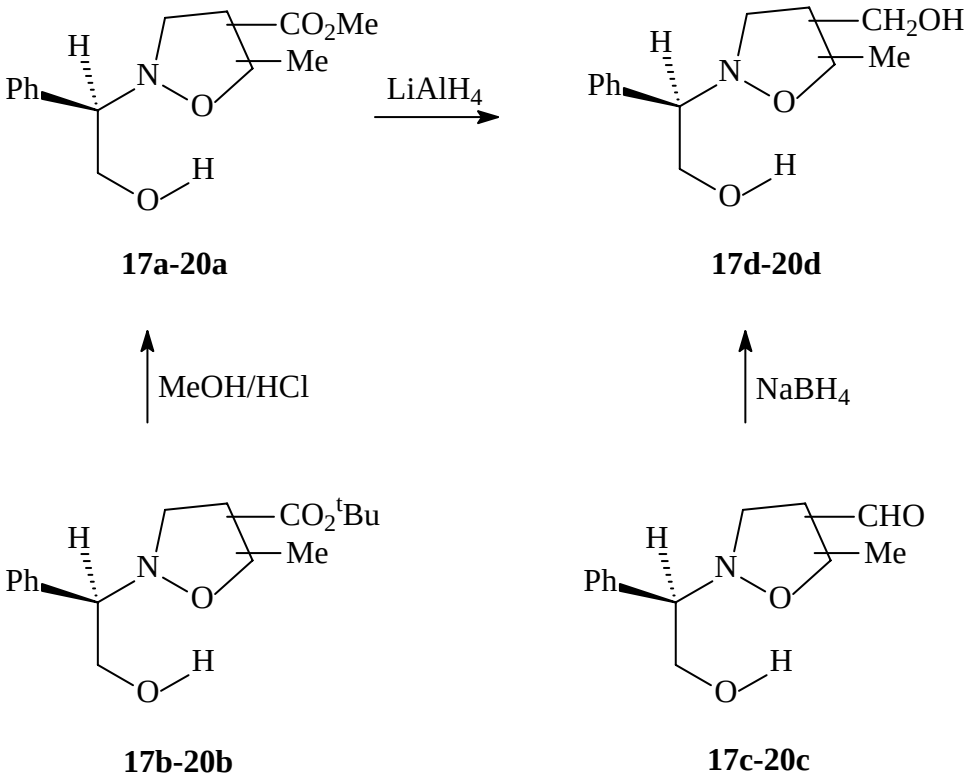
Scheme 53

Table 5.
Stereochemistry of cycloaddition[a] of the nitrone **7** with 1,2 disubstituted alkenes

Alkene **11**	% composition of adducts				Regioisomeric distribution	Isolated yields(%)
	17	**18**	**19**	**20**	**(17+18)/(19+20)**	
a	57	9	16	18	66:34	78
b	53	9	16	22	62:38	82
c	32	26	23	19	58:42	90
d	38	7	10	45	45:55	89
e	50	13	30	7	63:37	79
f	72	10	12	6	82:18	85
g	76	7	12	5	83:17	85

[a]Cycloadditions were carried out in toluene at 85°C for 12 h.

Tert-butyl crotonate (**12b)** addition to nitrone **7** gave a mixture of four isomers **17b-20b** in a ratio of 53:9:16:22 as determined by methyl signals in toluene d_8 which appeared as doublet at 1.22 (*J* 6.40 Hz) 1.19 (*J* 6.10 Hz), 0.89 (*J* 6.70 Hz), 0.85 (*J* 6.70 Hz) ppm, respectively. Ester exchange of the adduct **17b-20b** into isomers **17a-20a** revealed the same ratio as analyzed before.



Scheme 54

Cycloaddition of the chiral nitrone **7** to crotonaldehyde (**12c**) gave a mixture of adducts **17c-20c** which could not be purified by silica gel chromatography due to the unstable mixture of the compounds. The crude reaction mixture, however, on $NaBH_4$

reduction afforded a mixture of cycloadducts **17d-20d** which was purified and analyzed by NMR spectroscopy (*vide infra*) which revealed the presence of the diols **17d-20d** in a ratio of 32:26:23:19, respectively.

Cycloaddition of the chiral nitrone **7** to crotonyl alcohol (**12d**) gave a non separable mixture of adducts **17d-20d** in 89% yield. The mixture of alcohols was analyzed by ^{1}H NMR which revealed the presence of the C(5)-methyl protons of **17d** and **18d**, and C(4)-methyl of **19d** and **20d** at δ1.35 (br, overlapping), 1.36 (d, *J* 6.1), 1.09 (d, *J* 6.8), 1.06 (d, *J* 6.4), ppm, respectively, in a ratio of 38:7:10:45, respectively, as determined by peak heights as well as integration of the signals. In order to correlate the stereochemical assignment a mixture of the cycloadducts **17a-20a** in a known ratio of 58:14:11:17 was reduced with $LiAlH_4$ and the resultant non separable mixture of alcohols was analyzed by ^{1}H NMR ($CDCl_3$, +20°C) spectroscopy which revealed the presence of the **17d** - **20d** in an almost similar ratio of ~58:14:11:17.

Cycloaddition of the chiral nitrone **7** to *trans*-methyl γ–hydroxycrotonate **12e** gave a non separable mixture of adducts **17e-20e** in a ratio of 50:13:30:7, respectively, as determined by ^{1}H NMR integration or peak heights of the CO_2Me singlets which appeared at δ3.70 (for **18e**), 3.72 (for **17e**), 3.82 (for **19e**), and 3.88 (for **20e**). The down field singlets were attributed to the C(5)-CO_2Me of **19e** and **20e** because of their proximity to the ring oxygen**,** while the upfield singlets were assigned to the C(4)-CO_2Me of **17e** and **18e**.

Cycloaddition of nitrone **7** with methyl cinnamate **12f** gave a mixture of four isomers **17f-20f** as indicated by the presence of four methyl singlets at δ3.73, 3.71, 3.82,

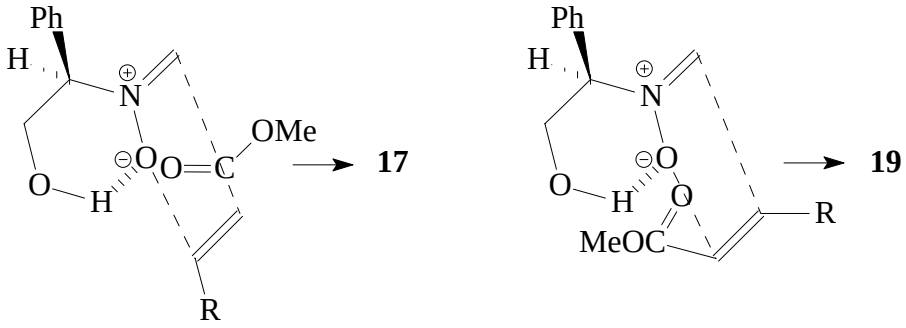
and 3.80 ppm, respectively. The phenyl group at C-5 was indicated by the presence of signals at δ5.50 (major) and 5.30 (minor) which are assigned to the C5(H) in similar cases.[94] The spectrum in toluene-d_8 revealed the presence of the corresponding methyl singlets free of any overlapping signals at δ3.24**,** 3.20, 3.32, 3.30 ppm in a ratio of 72:10:12:6 for the isomers **17f-20f**, respectively. The downfield methyl singlets were attributed to the C-(5)-CO_2Me signals as a result of their proximity to the ring oxygen. As previously noted in nitrone-cinnamate cycloadditions,[94] the major product is assigned with *endo*-oriented CO_2Me. As a result of nitrogen inversion, most of the NMR signals were very broad.

The reaction of *tert*-butyl cinnamate **12g** to nitrone **7** afforded the cycloadducts **17g-20g.** The t-butyl proton signals for **17g-20g** appeared at δ1.44, 1.43, 1.52, 1.47 ppm, respectively in a ratio of 76:7:12:5 and the stereochemisty was correlated to the methyl cinnamate adducts **17f-20f** by converting the former to the later by transesterification with methanolic HCl.

As evident from the Table 5, the addition of crotonates **12a-c,e** containing electron withdrawing conjugated substituents (i.e. CO_2R, CHO) lead to adducts favouring the regioisomers **17** and **18** over **19** and **20** by a ratio of ~60:40, while the cinnamates **12f,g** demonstrated higher preference for the corresponding regiomers in a ratio of ~80:20. It indicates the higher preference for the C-terminal of the nitrone to attach itself to the alkene end containing the conjugated substituents. In the addition of **12d**, the regiochemical preference is lost due to the presence of normal substituents (i.e. CH_3 vs. CH_2OH) at both ends of the alkene; a regioisomeric ratio of 45:55 was obtained.

The major adduct was assigned the stereochemistry as in **17** with *endo*-oriented C=O or CH_2OH as a result of favorable secondary orbital interactions.

Stereoisomeric preference for the *endo*-oriented CO_2R in isomers **17** over *exo*-oriented CO_2R in **18** was found to be much higher than that in their regioisomeric counterparts **19** and **20** (Table 5). A look at the corresponding transition states **A** and **B** might reveal the reasons for such differences. In transition state **A** the OMe group does not experience steric crowding as much as in transition state **B** where the OMe group will be subjected to non-bonded repulsions with the substituent at the nitrogen.



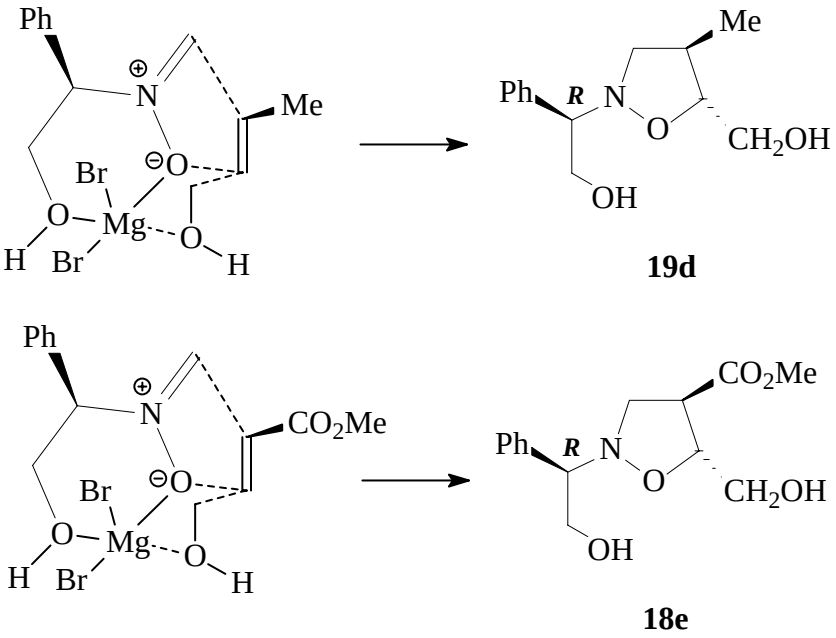
A: α–*endo*(CO_2Me) **B:** α–*endo*(CO_2Me)

Scheme 55

3.3.1 1,3-DC reaction of chiral nitrone 7 with 1,2-disubstituted alkenes (12) in the presence of some *Lewis* acids

Cycloaddition reaction of the chiral nitrone **7** with methyl crotonate (**12a**), crotyl alcohol (**12d**) and *trans*-methyl γ–hydroxycrotonate (**12e)** were carried out in the presence of Lewis acid catalysts like $BF_3.OEt_2$, $ZnCl_2$, $Ti(O^iPr)_4$, $MgBr_2$ (Scheme 53). The stereochemical analyses are given in Table 6. As evident from the Table the addition of crotyl alcohol in the presence of one equivalent of $MgBr_2$ becomes regiospecific resulting in the formation of the isomers **19d** and **20d** in a ratio of 91:9, respectively. It is to be mentioned that the reaction in the absence of $MgBr_2$ gave all four possible isomers (Table 6). In the non-catalytic reaction, the ratio of **19d** and **20d** was 10:45 (i.e. 18:82), while the ratio changed to 91:9 in the catalytic reaction – a reversal in the regio- as well as stereoselection was thus observed.

We carried out the cycloaddition of **7** with **12e** in the presence of one equivalent of $MgBr_2$. with the anticipation that it would lead to adducts with CO_2Me group at the C(4) position. This was indeed found to be the case; the addition reaction was regiospecific resulting in the formation of the isomers **17e** and **18e** in a ratio of 19:81, the regioisomeric adducts **19e** and **20e** were not formed. The results thus obtained can be explained as before with the transition state as depicted in Scheme 56 in which CH_2OH group assumes *endo*-orientation prior to cycloaddition reaction.


Ph
N
Me
Br
O
O
Mg
H
Br
O
H
Ph
R
N
O
Me
CH2OH
OH
19d
Ph
N
CO2Me
Br
O
O
Mg
H
Br
O
H
Ph
R
N
O
CO2Me
CH2OH
OH
18e

Scheme 56

Table 6.
Stereochemistry of cycloaddition of the nitrone **7** with 1,2 disubstituted alkenes **12** in the presence of *Lewis* acid

Alkene **12**	% composition of adducts **17**	**18**	**19**	**20**	Regioisomeric distribution **(17+18)/(19+20)**	Isolated yields(%)	*Lewis* Acid
a	57	9	16	18	66:34	78	none
	58	11	14	17	69:31	65	BF_3.OEt
	57	12	13	18	69:31	65	$Ti(O^iPr)_4$
	58	14	11	17	72:28	65	$ZnCl_2$
d	38	7	10	45	45:55	89	none
	0	0	91	9	0:100	95	$MgBr_2$
e	50	13	30	7	63:37	79	none
	19	81	0	0	100:0	76	$MgBr_2$
	18	82	0	0	100:0	80	$MgBr_2$, IPA[a]

[a]Reaction was carried out in the presence of one equivalent isoprpy alcohol (IPA)

The result discussed above are in general agreement with the frontier orbital treatment of the nitrone 1,3-dipolar cycloadditions.[4,82-87] In the case of 1,2-disubstituted alkenes both the HOMO-LUMO combinations do not offer any regiochemical preference since the nitrone as well as the alkene HOMO orbitals have similar magnitude of orbital coefficients at both the terminals of the nitone[88,89] and alkenes.[90] As such a mixture of regioisomers are expected to be formed in the addition reactions of methylene nitrones with 1,2-disubstituted alkenes.

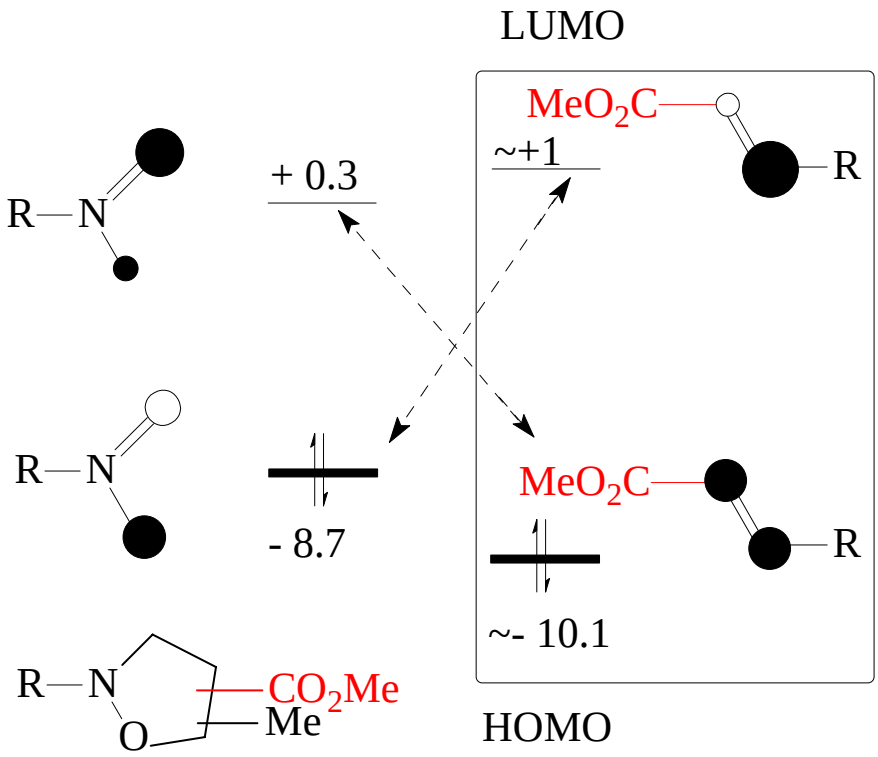
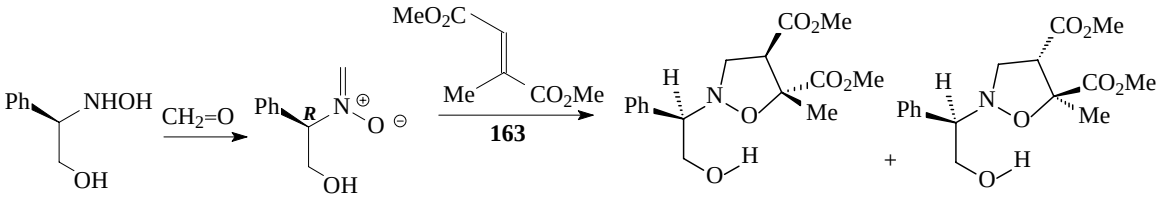


Figure 7. Frontier Orbital energies of nitrone and crotonates

3.4 1,3-DC reaction of chiral nitrone 7 with tri-substituted alkenes (163)

Cycloaddition of the nitrone **7** with the trisubstituted alkene dimethyl mesaconate (**163**) afforded the cycloadducts **164** and **165** in a ratio of 80:20. The regioisomeric products with the oxygen terminal of the nitrone attaching itself to the less substituted end of the alkene were not formed. Major adduct was assigned the stereochemistry as in **164** since its formation will involve the transition state which will be sterically favored as a result of *exo*-disposition of two of the three alkene-substituents.



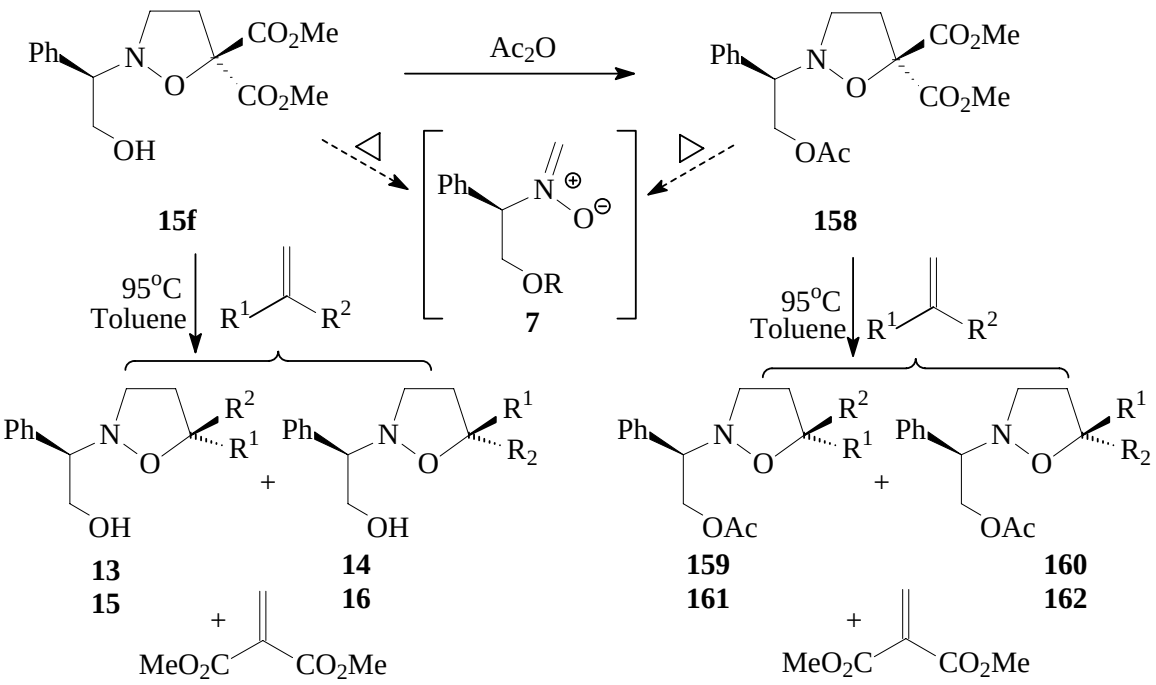
7 **164** **165**

Scheme 57.

3.5 Cycloreversion of the adducts 15f/158 and trapping the nitrone 7 with alkenes

The cycloadduct **15f** and its acetyl derivative **158** were subjected to undergo cycloreversion in toluene at 95°C. The similar adducts of dimethyl methylenemalonate and usually the adducts from electron deficient alkenes are known to undergo cycloreversion very readily[9].

The objective of this study is to investigate the effect of H-bonding on the stereochemistry of the cycloaddition reaction. The adduct **15f** on cycloreversion would generate the chiral nitrone (**7**, R=H), while the adduct **158** is expected to give the acetyl nitrone **7** (R=Ac). The addition of these nitrones (**7**, R=H; R=Ac), under similar conditions would reveal the effects of the presence and absence of the H-bonding on the stereochemistry of the cycloadditions. As evident from Table 7, the effect of H-bonding is amply demonstrated in the addition of styrene which trapped the nitrone **7** on thermolysis. While the nitrone **7** (R=H) gave the isomers **13a** and **14a** in a ratio of 70:30, the corresponding nitrone **7** (R=Ac) afforded **159** and **160** in a ratio of 50:50. The presence of H-bonding thus makes the addition of the nitrone **7** (R=H) more stereoselective than its acetyl counterpart **7** (R=Ac) at least in the case of styrene. However, such difference in the stereoselection was not observed in the cycloreversion process in the presence of methyl acrylate and methyl methacrylate (Table 7)



13a , 14a (R^1=H; R^2 = Ph)

13c , 14c (R^1=H; R^2 = CO_2Me)

15b , 16b (R^1=CO_2Me; R^2 = Me)

159a , 160a (R^1=H; R^2 = Ph)

159c , 160c (R^1=H; R^2 = CO_2Me)

161b , 162b (R^1=CO_2Me; R^2 =Me)

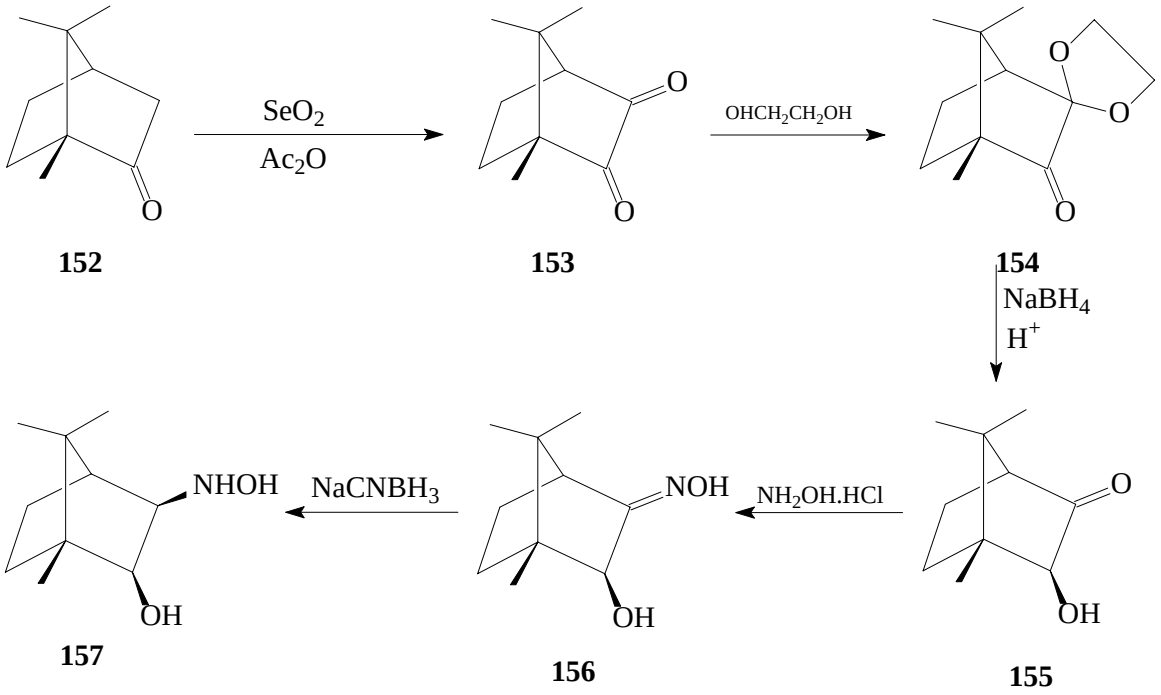
Scheme 58

Table 7.
Regio- and stereo- chemistry of the cycloreversion [a] of the cycloadduct **15f** and trapping the nitrone **7** with alkenes

Adduct/alkene	% composition of adducts[c]		%Exchanged[b] (Isolated yield%)
15f/styrene	**(13a)** 70	**(14a)** 30	50 (35)
158/styrene	**(159a)** 50	**(160a)** 50	50 (37)
15f/methyl acrylate	**(13c)** 42	**(14c)** 58	90 (60)
158/methyl acrylate	**(159c)** 36	**(160c)** 64	90 (63)
15f/methyl methacrylate	**(15b)** 80	**(16b)** 20	70 (60)
158/methyl methacrylate	**(161b)** 80	**(162b)** 20	67 (58)

[a]Reactions were done in toluene for 24 h at 95°C.
[b]The reaction mixture contained the unreacted starting adducts **15f/158**.
[c]Adducts are written in parentheses

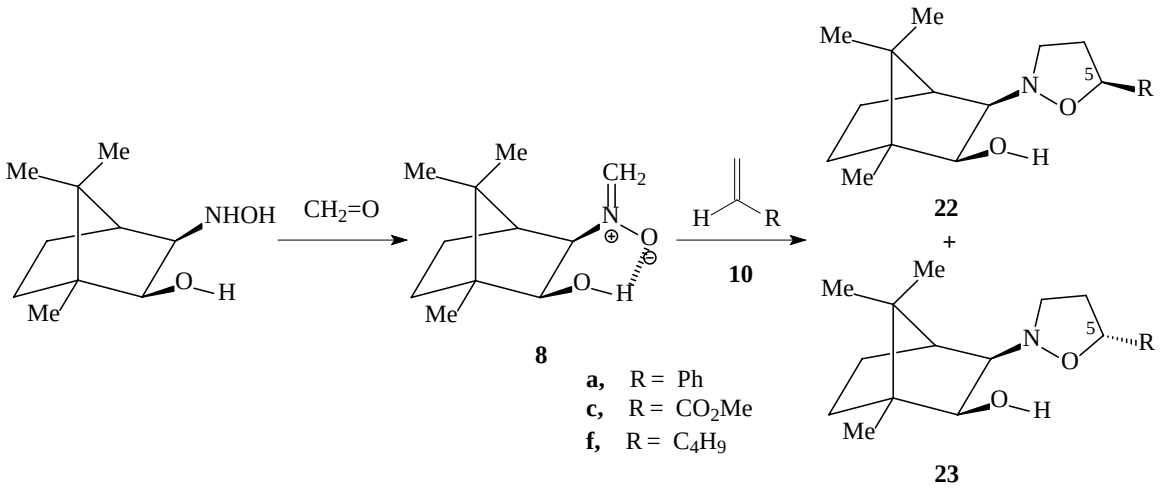
3.6 Preparation of chiral nitrone 8 and its 1,3 DC reactions with alkenes



152 **153** **154** **155** **156** **157**

Scheme 59

Hydroxylamine **157** was prepared from D-camphor **152.** Oxidation of camphor **152** by selenium dioxide gave camphoroquinone **153** which was protected with ethylene glycol to give **154** (Scheme 59)**.** Reduction of **154** with sodium borohydride followed by deprotection afforded **155** which on reaction with hydroxylamine hydrochloride gave the oxime **156**. Hydroxylamine **157,** obtained by reduction of **156** with sodium cyanoborohydride, upon condensation with formaldehyde gave the chiral nitrone **8** (Scheme 60)**.**[95-98]



Scheme 60

Table 8.
Regio- and stereo- chemistry of the cycloaddition of the nitrone **8** with monosubstituted alkenes

Alkene **10**	Temp (°C)	Time (h)	Solvent	% composition of adducts **22**	% composition of adducts **23**	Isolated yields (%)
a	50	6	$CHCl_3$	96	4	66
c	50	6	$CHCl_3$	65	35	83
f	85	8	toluene	95	5	75

Addition of styrene to the nitrone **8** gave a non separable mixture of adducts **22a** and **23a** in a ratio of 96:4 as determined by integration of C(5)H signals (Scheme 60). The major adduct is assigned the stereochemistry as in **22a** which is expected to be the adduct formed *via* the sterically favored transition state having *exo*-oriented phenyl group. The addition of methyl acrylate to nitrone **8** afforded also a non separable mixture of the adducts **22c** and **23c** in a ratio 65:35. Crystallizations of the mixture afforded major cycloadduct **22c** as colorless needles which were analyzed by X-ray crystallography. ORTEP drawing of **22c** is shown below (Figure 8).

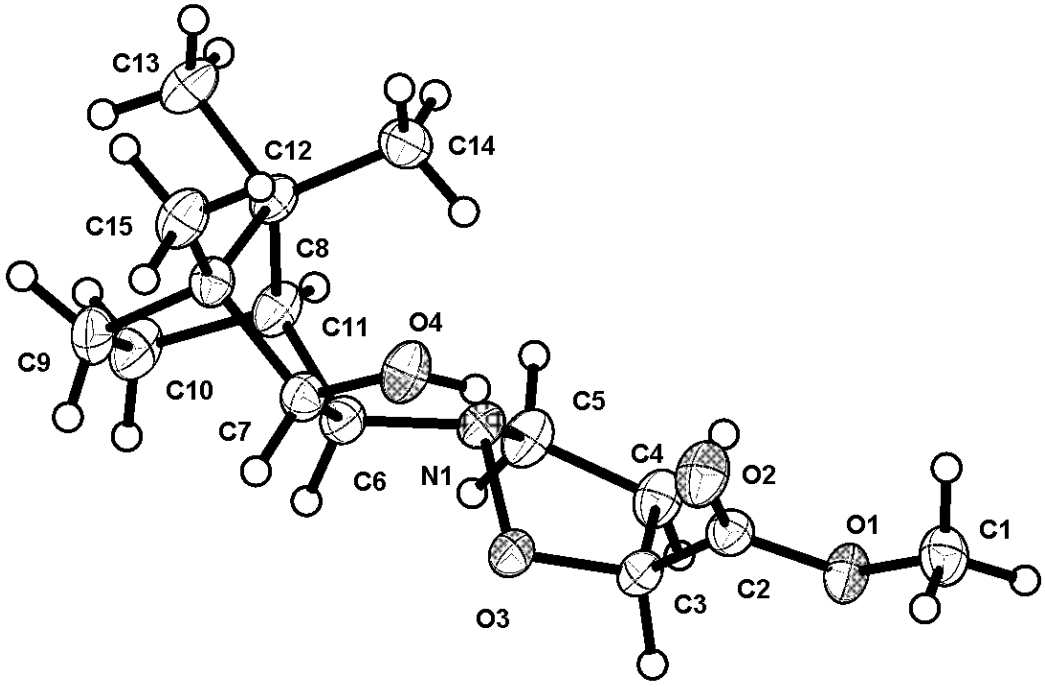
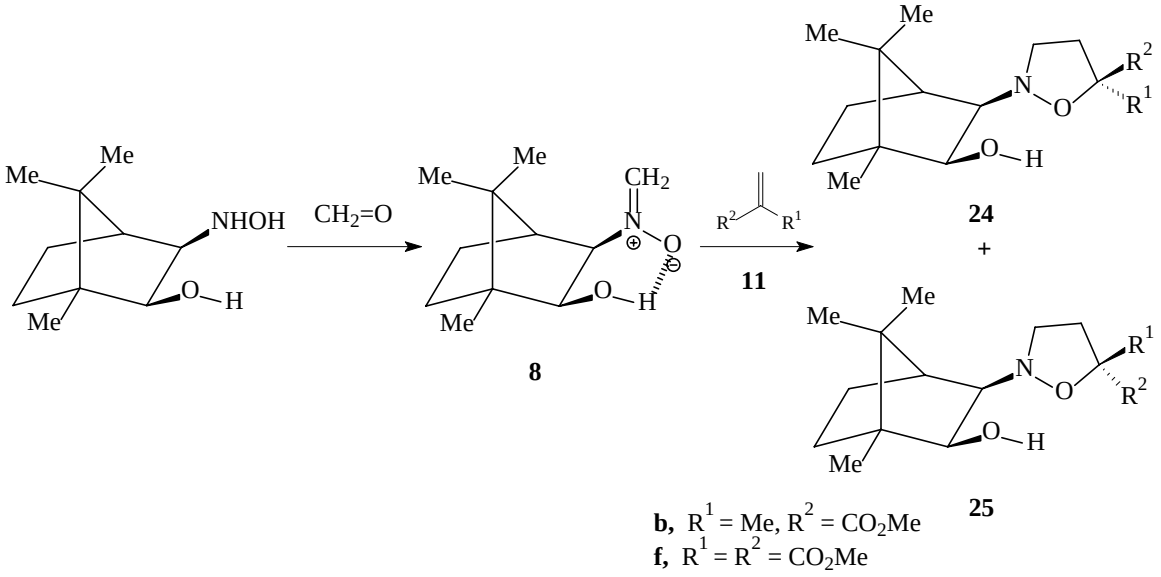


Figure 8. ORTEP drawing of **22c**

Cycloaddition of 1-hexene with nitrone **8** gave a mixture of the cycloadducts **22f** and **23f** in a ratio of 95:5 as determined by the peak height of the methyl singlets for the major isomer at δ0.78, 0.97, 1.17 ppm and minor at δ0.82, 0.99 and 1.09 ppm. The major adduct was assigned the stereochemistry as in **22c** formed *via* transition state having *exo*-oriented n-butyl group (Scheme 60).



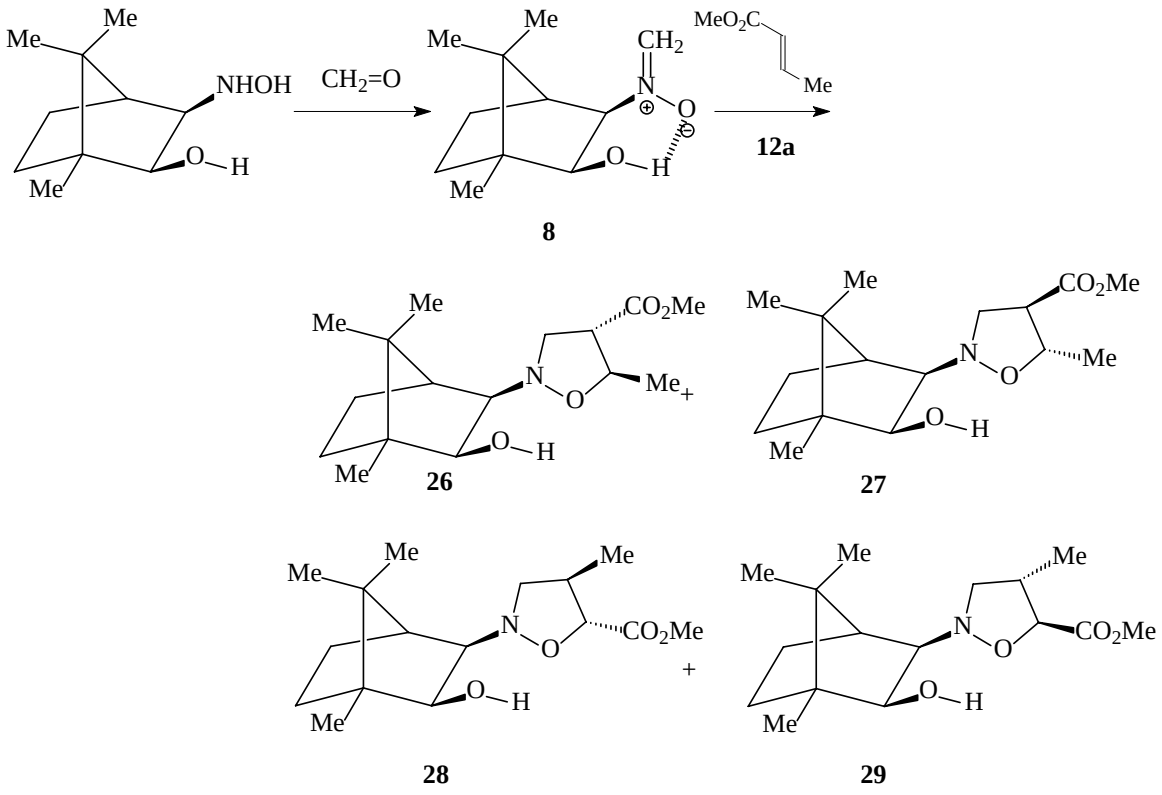
Scheme 61

Table 9.
Regio- and stereo- chemistry of the cycloaddition of the nitrone **8** with 1,1-disubstituted alkenes

Alkene **11**	Temp (°C)	Time (h)	Solvent	% composition of adducts **24**	% composition of adducts **25**	Isolated yields (%)
b	50	6	$CHCl_3$	66	34	88
f	50	6	$CHCl_3$	100		79

The reaction of nitrone **8** with methyl metacrylate afforded a mixture of the adducts **24b** and **25b** in a ratio of 66:34 as determined by integration of methyl proton signals in

^{1}H-NMR spectrum of the crude reaction mixture (Scheme 61). Reaction of nitrone **8** with dimethyl methylenemalonate **11f** gave the cycloadduct **24f** as the sole regiomer.



Scheme 62

Table 10.
Regio- and stereo- chemistry of the cycloaddition of the nitrone **8** with methyl crotonate **12a**

Solvent	Temp (°C)	Time (h)	% composition of adducts				Isolated yields (%)
			26	**27**	**28**	**29**	
$CHCl_3$	50	12	63.6	3.4	29	4	77

Addition of *trans*-methyl crotonate **12a** to nitrone **8** gave adducts **26-29** (Scheme 62). The diastereomeric ratio of major **26** and minor isomer **27** was found to be around

95:5, respectively, as determined by integration of C5(H) signals of the major and minor isomer at δ4.48 ppm and 4.18 ppm, respectively. Careful proton NMR analysis of the crude sample and the separated fraction revealed the presence of **28** and **29** in a ratio of 88:12, respectively. The regioisomeric ratio of (**26** + **27**) and (**28** + **29**) was found to be 67:33, respectively.

CHAPTER 4

CONCLUSION

Cycloaddition reactions of chiral methylene nitrones **7** and **8** with a variety of mono-, di- and tri-substituted alkenes have been carried out in detail. Champhor derived nitrone **8** showed better selectivity in comparison with the phenyl glycinol nitrone **7**. The stereochemical control observed in these reactions has been explained in terms of steric factor and secondary orbital interaction in the transition states. The β-face of the H-bonded nitrone **8** is more crowded than that of the nitrone **7.** As such the nitrone **8** is expected to demonstrate greater selectivity towards attack by alkenes on it's α-face having alkene substituent exo-oriented due to steric factor or endo-oriented due to secondary orbital interactions. The α-face of the nitrone **8** is also more crowded than that of the nitrone **7;** the nitrone **8** thus showed greater preference for the α-exo approach of the alkenes.

The studies of cycloreversion of some cycloadducts have shown the effect of hydrogen bonding. While cycloaddition of glycinol nitrone **7** to styrene gave adducts in a ratio of 70:30, the cycloaddition of the acetyl derivative of nitrone **7** gave adducts in 50:50 ratio.

Metal chelated nitrone cycloadditions have demonstrated remarkable regio- and stereoselectivity which can be explained by considering the metal chelated nitrone transition state. Not only the metal chelated dipolar cycloaddition reaction improved the stereoselection, in some cases it led to regioreversion.

The findings of the study would indeed be useful in incorporating chiral centers in natural product synthesis.

CHAPTER 5

EXPERIMENTALS

Experimental

All m.p.s are uncorrected.. I.r. spectra were recorded on a Perkin Elmer 16F PC FTI.R spectrometer (Spectral resolution, 4 cm^{-1}; Number of scans, 4). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using TMS as internal standard on a JEOL LA 500 MHz spectrometer. NMR spectra of selected compounds were shown in appendix. Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Paraformaldehyde, 1-hexene, styrene, methyl acrylate, methyl methacrylate, methyl crotonate, methylallyl alcohol, corotnaldehyde, methyl cinnamte, m-chloroperbenzoic acid (70% purity), D(-)-α–phenylglycinol, hydroxylamine hydrochloride from Fluka were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. $MgBr_2$ was prepared freshly by reaction of Mg with 1,2-dibromoethane. *Trans*-methyl γ–hydroxycrotonate[99]and dimethyl methylenemalonate[100] were prepared as described in the literature.

5.1 Preparation Chiral Hydroxylamines 151

4-methoxybenzaldehyde (**147**).

Sodium metal (5.0 g, 217 mmol was added to ethanol (150 mL), portion wise) after which *p*-hydroxybenzaldehyde **146** (20.0 g, 164 mmol) was added and stirred at room temperature for 15 minutes. CH_3I (15 cm^3) was then added and the dark brown reaction mixture was stirred in a closed vessel at 60-65°C for 24 h. The reaction mixture was concentrated and the residual liquid was diluted with water (50 cm^3) and extracted with ether (100 cm^3). The organic layer was then dried (Na_2SO_4), concentrated and distilled under vacuum (0.3 mbar, 70°C) to afford **147** (19.2 g, 86%) as a colorless liquid.

2-[(4-methoxybenzylidene)amino]-2-phenylethanol (**149)**

A mixture of $MgSO_4$ (12.6 g), dichloromethane (26 cm^3), D-(-)-α-phenylglycinol [(2*R*)-2-amino-2-phenylethanol] (**148**) (4.8 g, 35 mmol) and *p*-anisaldehyde (5.42 g, 39.8 mmol) was stirred under nitrogen at 20°C for 24 h. The reaction mixture was filtered through $MgSO_4$ pad and washed with CH_2Cl_2. A small portion of the residual liquid was crystallized from ether-pentane to give **149** as colourless needles**.** δ_H($CDCl_3$, +20°C) 3.84 (3H, s), 3.91 (1H, m), 3.94 (1H, m), 4.45 (1H, dd, *J* 4.45 and 8.4 Hz), 6.91 (2H, d, *J* 8.85), 7.33 (5H, m), 7.71 (2H, d, *J* 8.85), 8.30 (1H, s); δ_C($CDCl_3$, 20°C) 55.6, 67.8, 76.1, 113.9 (2C), 126.4, 127.5(2C), 128.6, 128.9(2C), 130.1(2C), 140.9, 161.9, 162.1 (TMS: 0.0; $CDCl_3$ middle carbon:77.02).

(2*R*)-2-(hydroxyamino)-2-phenylethanol (**151)**

MCPBA (7.22 g, mmol) was added portion wise (*ca.* 5 min) at 0°C to the stirring solution of the crude imine **149** in CH_2Cl_2 (150 cm^3) under N_2. At the end of the addition, the reaction mixture was kept at 20°C for 2 h. The organic layer was washed with 1% Na_2SO_3 solution (80 cm^3) and 20 % K_2CO_3 solution (2x25 cm^3). The combined aqueous layer was reextracted with CH_2Cl_2 (3x25 cm^3). The combined organic layers were combined with the previous CH_2Cl_2 layer, dried (Na_2SO_4) and concentrated. Hydroxylamine hydrochloride (3.46 g, 52.7 mmol) was added to the residual liquid in absolute ethanol (45 cm^3) at 0°C and stirred using a magnetic stir-bar for overnight. The mixture was then allowed to warm to room temperature after which CH_2Cl_2 (70 cm^3) was added and the stirring was continued for 2 h. The mixture was filtered to remove the excess $NH_2OH.HCl$. The filtrate was concentrated and the residual liquid was taken up in ether (30 cm^3) and washed with water (2x30 cm^3). The organic layer contained the anisaldehyde-oxime. The aqueous layer was saturated with K_2CO_3 and extracted with ether (2x25 cm^3). The organic layers was dried (Na_2SO_4), concentrated and chromatographed with ether/methanol as eluent to give **151** as a solid **(**4.29 g, 80 %); ν_{max} (KBr) 3358(broad), 3036, 2921, 2881, 1651, 1495, 1455, 1061, 1028, 873, 760 and 700 cm^{-1}; δ_H($CDCl_3$, +20°C) 3.79 (2H, m), 4.05 (1H, dd, *J* 4.25 and 7.3 Hz), 4.6-6.5 (1H, broad), 7.28 (5H, m); δ_C($CDCl_3$, 20°C) 63.46, 67.61, 127.86 (2C), 128.08, 128.64 (2C), 138.03) (TMS: 0.0; $CDCl_3$ middle carbon: 77.04)

5.2 Preparation Chiral Hydroxylamines 157

(1R)-(-)-Camphorquinone (**153**)[95]

To a solution of (1R)-(+)-Camphor (D-Camphor) **152** (30.0 g, 197 mmol) in acetic anhydride (30 cm^3) was added SeO_2 (36.0 g, 325 mmol) and the reaction mixture was stirred using a magnetic stir bar at 140-150°C for 4 h. The mixture was then cooled, filtered and washed with acetic acid (20 cm^3) and the filtrate was carefully neutralized with a 50 wt% KOH solution (~1 mol of KOH is required). The aqueous mixture was extracted with ether (3x50 cm^3), dried over Na_2SO_4, and crystallized from hexane/ether to give **153** (22.5 g, 68 %) as colorless crystals, mp. 198-199°C (Lit. mp[95] 198°C); δ_H($CDCl_3$, +20°C) 0.94(3H, s), 1.06(3H, s), 1.11(3H, s), 1.65(2H, m), 1.92(1H, m), 2.18(1H, m), 2.64(1H, d, *J* 5.45 Hz).

3,3-*Ethylenedioxycamphor* (**154**)[96]

[(1*S*,4*R*)-4,7,7-trimethyl-3*H*-spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-3-one]

(1R)-(-)-Camphorquinone (**153**) (22.5 g, 135.4 mmol), ethylene glycol (16.9 g, 272.3 mmol) and p-toluene sulphonic acid (1 g, 5.3 mmol) in benzene (125 cm^3) was heated under reflux in a Dean-Stark apparatus for 17h at 110°C, after which 4.4 cm^3 of water was collected. The reaction mixture was washed with dilute NaOH solution (1%) (40 cm^3) and water (30 cm^3), dried (Na_2SO_4) and evaporated. The residue gave the acetal **154** as colorless crystals, m.p. 82-85°C (ethanol); Lit. mp[96] 88°C. A second crop was obtained by dilution of the mother liquors with water (total mass of the acetal 14.3 g, 50 %) δ_H($CDCl_3$, +20°C) 0.91(3H, s), 0.98(3H, s), 1.02(3H, s), 1.59(2H, m), 1.81(1H, m), 1.96 (2H, m),

3.98 (1H, dd, *J* 7, 12.2 Hz), 4.02 (1H, dd, *J* 7, 12.2 Hz), 4.18 (1H, dd, *J* 7, 12.2 Hz), 4.29 (1H, dd, *J* 7, 12.2 Hz).

exo-2-*Hydroxyepicamphor* (**155**)[96]

[(1*S*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one] (**155**)

The acetal (**154**) (14.3 g, 68 mmol) in ether (30 cm^3) and methanol (30 cm^3) was cooled to about 5°C in an ice-bath and sodium borohydride (2.49 g, 65.8 mmol) was added. The mixture was stirred using a magnetic stir bar in an ice-bath for 30 min while an exothermic reaction took place, and then kept at 0°C for a further 2.5 h. It was washed with water several times and the ether was evaporated off to leave an oil which was cooled to about 5°C and mixed with ice-cold concentrated sulphuric acid-water (1:1; 44 cm^3). After 15 min, ice (25 g) was added and the mixture was extracted several times with ether. Evaporation of the ether and crystallization of the residue from n-hexane gave, in several crops, **155** (9.3 g, 74.6 %) as a powder, m.p. 226-228°C; (Lit. mp[96] 228-230°C).

exo-2-*Hydroxyepicamphor 3-oxime* (**156**)[97]

(1*S*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime

To a solution of hydroxylamine hydrochloride (11.3 g, 162.6 mmol) and sodium acetate (33.8 g, 312.2 mmol) in water (75 cm^3) was added hydroxyketone (**155**) (9.2 g, 54.7 mmol) in absolute ethanol (150 cm^3). The mixture was refluxed for 1 h. After removal of most of the ethanol by a gentle stream of N_2, the residual liquid was basified with 20 % of K_2CO_3 solution and extracted with ether (2x100 cm^3). The organic layer was dried

(Na_2SO_4) and evaporated to give a residue (10.2 g, ~ 99%) which was used without further purification in the subsequent step.

(1*R*,2*S*,3*R*,4*S*)-3-(hydroxyamino)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (**157**)[98]

To a stirred solution of oxime (**156**) (10.2 g, 55.7 mmol) in methanol (80 cm^3) was added of methyl orange (indicator, 6 mg) and 2N HCl to turn the indicator red (approx. pH 3). Sodium cyanoborohydride (4.4 g, 70 mmol) in methanol (10 cm^3) was added drop wise at 20°C with concurrent addition of HCl to keep the mixture at pH 3. The mixture was then stirred for 3 h. After removal of most of the methanol by a gentle stream of N_2, the residual liquid was basified with 20% K_2CO_3 solution and extracted with ether (3x50 cm^3). The combined organic layers was dried (Na_2SO_4), concentrated and purified by flash chromatography using hexane/ether as eluant. Crystallization from CH_2Cl_2/hexane gave, in several crops, hydroxylamine **157** as a colorless crystal (total 3.5 g, 34 %) m.p. 146-149 °C; $\nu_{max.}$ (KBr) 3458, 3341, 3133, 2942, 2876, 1461, 1418, 1362, 1240, 1146, 1048, 907 and 786 cm^{-1}; δ_H($CDCl_3$, +20°C) 0.77 (3H, s), 0.94(3H, s), 1.04(3H, s), 1.11(2H, m), 1.46(1H, m), 1.71(2H, m), 3.21(1H, d, *J* 7.3 Hz), 3.70(1H, d, *J* 7.05 Hz); δ_C($CDCl_3$, +20°C) 12.19, 22.34, 22.50, 28.10, 33.86, 47.28, 50.13, 50.81, 71.73, 80.96 (TMS: 0.0; $CDCl_3$ middle carbon: 77.1)

5.3 Cycloaddition of nitrone 7 to monosubstituted alkenes

5.3.1 Cycloaddition of nitrone 7 to styrene (10a)

To a solution of the hydroxylamine **151** (306 mg, 2.0 mmol) in $CHCl_3$ (15 cm^3) was added paraformaldehyde (75 mg, 2.5 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter $MgSO_4$ (200 mg) was added followed by styrene (1.5 cm^3). The reaction mixture was stirred in a closed vessel at 50°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using ether/hexane as eluent to give a non separable mixture of the cycloadducts **13a** and **14a** (483 mg, 90%) as a colorless liquid. Major and minor isomers were found in a ratio of 73:27 as determined by integration of the C5(H) signals.

$\nu_{max.}$ (neat) 3417, 3061, 3029, 2881,1603, 1493, 1454, 1360, 1310, 1179, 1028, 950, 913, 847, 760, and 703 cm^{-1}; δ_H($CDCl_3$, +20°C) Broad NMR signal between δ2.2-5.5 ppm. The proton signals for the individual isomers, as detailed below, are extracted from the spectra of non separable mixture of the cycloadducts.

Major isomer 13a : δ_H($CDCl_3$, -40°C) 2.20 (1H, m), 2.77 (1H, m), 2.98 (1H, m), 3.28 (1H, m), 3.70 (1H, OH), 3.76 (1H, m), 4.05 (1H, m), 4.22 (1H, m), 5.39 (1H, dd, *J* 6.6 and 8.1 Hz), 7.40 (10H, m). C5(H) signal for minor invertomer appear at 4.97 ppm (t, *J* 7.5 Hz) in a ratio of 95:5; δ_C($CDCl_3$, -40°C) 38.74, 53.94, 68.73, 70.83, 78.93, 128.8(2C) and 129.8(2C), 137.68 and 140.59. (TMS : 0.0; $CDCl_3$ middle carbon: 77.1). The spectrum also revealed the presence of weak signals for the minor invertomer.

Minor isomer 14a : δ_H($CDCl_3$, -40°C) 2.1 (1H, m), 2.6 (1H, m), 2.65 (1H, m), 3.15 (1H, m), 3.55 (1H, m), 3.70 (1H, OH), 4.00 (1H, m), 4.17 (1H, m), 5.16 (1H, dd, *J* 6.9 and 8.1

Hz), 7.4 (10H, m). C5(H) signal for minor invertomer of minor isomer appear at 4.72 ppm (t, *J* 7.1 Hz) in a ratio of 92:8; δ_C($CDCl_3$, -40 °C) 36.26, 55.07, 68.42, 74.17, 80.22, 128.8-129.8 overlapping signals of aromatic carbons at 137.57 and 140.13. (TMS : 0.0; $CDCl_3$ middle carbon: 77.1). In addition to these signals, signals for the minor invertomer can also be seen in the spectrum.

The above cycloaddition reaction was repeated at 0° and 25°C using the hydroxylamine **151** (38 mg, 0.25 mmol). In each case the relative proportion of the other reactants was similar to the one carried out at 50°C. However, the nitrone-$MgSO_4$ mixture was brought to the required temperatures i.e 0° and 25°C after which the appropriate amount of styrene was added. The reactions at 0° and 25°C were carried out for duration of 6 and 3 days, respectively. Usual work up as above and flash chromatography using 20:1 CH_2Cl_2/methanol mixture afforded the isomers at 0° and 25°C in 65 and 75% yields, respectively. Integration of several proton signals in ^{1}H NMR in $CDCl_3$ indicated the ratio of the isomers as 76:24 in both cases.

5.3.1.1 Cycloreversion of the cycloadduct 15f, and trapping of the nitrone 7 by styrene (10a)

A solution of **15f** (25 mg) and styrene (300 mg) in toluene (5 cm^3) was thermolyzed in a closed vessel under N_2 at 95°C for 24 h. After removal of the solvent and the alkenes, the residual liquid was analyzed by ^{1}H NMR which revealed the presence of **13a** and **14a** in a ratio of 70:30, respectively. The NMR spectrum also revealed the presence of the starting adducts (~25%).

Similar cylcloreversion was carried out with acetyl derivative **158** and the ratio was found to be 50:50 for **159a** and **160a**, respectively.

5.3.2 Cycloaddition of nitrone 7 to acrolein (10b), and sodium borohydride reduction of the cycloadducts 13b and 14b

To a solution of the hydroxylamine **151** (77 mg, 0.49 mmol) in $CHCl_3$ (5 cm^3) was added paraformaldehyde (30 mg, 1 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ (100 mg) was added followed by acrolein (80 mg, 1.43 mmol). The reaction mixture was stirred in a closed vessel at 50°C for 6 h under N_2, filtered, concentrated. The residual liquid containing the cycloadducts **13b** and **14b** was dissolved in methanol (5 cm^3) and $NaBH_4$ (100 mg) was added to the solution of the adducts, and stirred at room temperature for 1 hour. After removal of the solvent by gentle stream of N_2, the reaction mixture was basified by 20% K_2CO_3 (7 cm^3), extracted with CH_2Cl_2 (3x10 cm^3). The combined organic layers was dried (Na_2SO_4) to give a non separable mixture of the corresponding alcohol **13e** and **14e** in a ratio of 44:56 as determined by integration of non overlapping proton signals at δ2.08 (1H, m), 2.31 (1H, m) for the major **14e** , and at δ2.14 (2H, m) for minor isomer **13e**. The crude alcohol adducts was purified by silica gel chromatography using ether/methanol (95:5) as the eluent to give **13e** and **14e** in an overall yield of 65%.

5.3.3 Cycloaddition of nitrone 7 to methyl acrylate (10c)

To a solution of the hydroxylamine **151** (612 mg, 4.0 mmol) in $CHCl_3$ (15 cm^3) was added paraformaldehyde (145 mg, 4.8 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ (400 mg) was added followed by methyl acrylate (1.5 cm^3). The reaction mixture was stirred in a closed vessel at 50°C for 6 h under N_2, filtered, concentrated and the residual liquid was chromatographed over silica using ether/hexane as eluent to give the minor isomer **13c** (381 mg, 37.9 %) as a colorless liquid. Continued elution afforded a mixture of **13c** and **14c** (191 mg, 19%) and finally the major isomer **14c** (296 mg, 29.4%) as colorless needles. The total isolated yield for the addition reaction was thus found to be 86.3%. The diastereomeric ratio of **13c** and **14c** was found to be around 46:54, respectively, as determined by integration of several proton signals in ^{1}H-NMR spectrum of the crude reaction mixture. The stereochemistry of the major isomer **14c** was assigned by X-ray diffraction analysis.

13c : $\nu_{max.}$ (neat) 3491, 3061, 3029, 2952, 2850, 1740, 1603, 1493, 1406, 1350, 1290, 1211, 1083, 937, 826, 760, and 703 cm^{-1}; δ_H($CDCl_3$, +20°C) 2.41 (1H, m), 2.55 (1H, m), 2.99 (1H, m), 3.28 (1H, OH), 3.76 (1H, m), 3.79 (3H, s), 3.95 (2H, m), 4.67 (1H, m), 7.33 (5H, m); δ_H($CDCl_3$, -40°C) 2.42 (1H, m), 2.61 (2H, m), 3.01(1H, m), 3.69 (1H, OH), 3.78 (1H, m), 3.83(3H, s), 3.99 (2H, m), 4.76 (1H, dd, *J* 4.0 and 9.5), 7.33 (5H, m); δ_C($CDCl_3$, -30°C) 32.3, 52.5, 52.7, 67.1, 71.3, 74.4, 127.9(2C), 128.1, 128.6(2C), 138.1, 173.1 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1). Proton and C-13 revealed the absence of a minor invertomer. The proton signals were sharp even at room temperature.

14c : $\nu_{max.}$ (KBr) 3481, 3088, 3063, 3024, 2982, 2942, 2904, 2876, 1740, 1496, 1452, 1433, 1364, 1316, 1299, 1279, 1209, 1172, 1111, 1081, 1057, 1023, 948, 915, 864, and 758 cm^{-1}; δ_H($CDCl_3$, +20°C) 2.41 (1H, m), 2.43 (1H, m), 2.91 (2H, m), 3.30 (1H, broad, OH), 3.75 (1H, m), 3.80 (3H, s), 3.96 (1H, dd, *J* 4.0 and 7.6 Hz), 4.17 (1H, dd, *J* 7.6 and 11.2), 4.56 (1H, m), 7.30 (5H, m); at -40°C the spectrum revealed the presence of invertomer in a ratio of 58:42

Major invertomer of 14c: δ_H($CDCl_3$, -40°C) 2.46 (2H, m), 3.12 (2H, m), 3.85 (3H, s), 3.65-4.40 (4H, complex m), 4.71 (1H, t, *J* 7.6 Hz), 7.30 (5H, m); δ_C($CDCl_3$, -30°C) 32.39, 48.90, 53.70, 68.70, 73.08, 76.68, 128.20(2C), 128.80(2C), 129.55, 138.26, 172.68 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

Minor invertomer of 14c: δ_H($CDCl_3$, -40°C) 2.46 (2H, m), 2.62 (1H, m), 2.92 (1H, m), 3.81 (3H, s), 3.65-4.40 (4H, complex m), 4.54 (1H,t, *J* 6.6), 7.30(5H, m) δ_C($CDCl_3$, -30°C) 33.01, 52.91, 53.01, 63.59, 68.87, 72.93, 127.69(2C), 128.20(2C), 128.80, 135.20, 174.12 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

The above cycloaddition reaction was repeated at 0° and 25°C using the hydroxylamine **151** (100 mg, 0.65 mmol). In each case the relative proportion of the other reactants was similar to the one carried out at 50°C. The reactions at 0° and 25°C were carried out for duration of 6 and 3 days, respectively. Usual work up as above and flash chromatography using 20:1 CH_2Cl_2/methanol mixture afforded the isomers at 0° and 25°C in 64 and 74% yields, respectively. Integration of several proton signals in ^{1}H NMR in $CDCl_3$ indicated the ratio of the isomers. The ratios were similar both in the crude reaction mixture and the

isolated products. The ratios were further confirmed by taking NMR in toluene-d_8 in which the methyl singlets of **13c** and **14c** appeared at δ3.32 and 3.30, respectively. The peak heights were used to calculate the compositions. The ratio of the **13c** and **14c** at 0° and 25°C were found to be 44:56 and 48:52, respectively. The ^{1}H NMR in toluene-d_8 of a known mixture of **13c** and **14c** from the earlier experiment validated the relation of the peak height to the composition.

5.3.3.1 Cycloreversion of the cycloadduct 15f and trapping of nitrone 7 by methyl acrylate (10c)

A solution of **15f** (25 mg) and methyl acrylate (300 mg) in toluene (5 cm^3) was thermolyzed in a closed vessel under N_2 at 95°C for 24 h. After removal of the solvent and the alkenes, the residual liquid was analyzed by ^{1}H NMR which revealed the presence of **13c** and **14c** in a ratio of 42:58, respectively. The NMR spectrum also revealed the presence of minor amount of the starting adducts (~25%).

Similar cylcloreversion was carried out with acetyl derivative **158** and the ratio was found to be 36:64 for **159c** and **160c**, respectively.

5.3.3.2 Conversion of the cycloadducts (13c and 14c) to (13e and 14e)

To a stirred solution of **13c** (100 mg, 0.40 mmol) in ether (15 cm^3) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. Reaction was completed in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture were added water (0.1 g), 10% NaOH solution (0.1 g) and water (0.4 g). The mixture was stirred for 1

hour and was then decanted and the residue washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using CH_2Cl_2/methanol 95:5 to give **13e** as a colorless liquid (85 mg , 95 %). **13e** : $\nu_{max.}$ (neat) 3300, 3060, 3026, 2920, 1602, 1492, 1453, 1270, 1188, 1034, 870, 846, 759 and 701cm^{-1}; $\delta_H(CDCl_3$, +20°C) 2.08 (1H, m), 2.31 (1H, m), 2.40-3.50 (4H, broad), 3.64 (1H, m), 3.75 (2H, m), 4.09 (1H, m), 4.43 (1H, m), 7.35 (5H, m)

The above procedure was repeated with **14c** to give the corresponding **14e** (81 mg, 91%) as a colorless liquid.

14e : $\nu_{max.}$ 3300, 3031, 2922, 2862, 1449, 1035, 754 and 701 cm^{-1}; $\delta_H(CDCl_3$, +20°C) 2.14 (2H, m), 2.25-3.50 (3H, br), 3.59-3.87 (4H, m) 4.10 (1H, m), 4.24 (1H, m), 7.31 (5H, m).

5.3.4 Cycloaddition of nitrone 7 to t-butyl methyl acrylate (10d)

Cylcoaddition reaction was carried out in $CHCl_3$ under similar conditions as before for the addition of methyl acrylate except that 0.5 mmol hydroxylamine **151** and 1 mmol of t-butyl methyl acrylate were used at 65°C for 6 h. Chromatography purification using ether/hexane as eluent gave the adducts as a colorless liquid in 85% yield. The NMR spectrum of the crude as well as the purified mixture revealed the presence of two isomers **13d** and **14d**.

ν_{max} : 3470, 3060, 2976, 2929, 2876, 1732, 1602, 1454, 1368, 1292, 1234, 1157, 1077, 915, 843, 732 $\alpha\nu\delta$ 704 cm^{-1}; $\delta_H(CDCl_3$, +20°C) 1.51 (9H, s), 2.30-2.50 (2H, m), 2.80-

3.00 (1H, m), 3.20-3.60 (1H, br), 3.72-3.77 (1H, m), 3.94-4.20 (2H, m), 4.40-4.55 (1H, m), 7.32 (5H, m).

5.3.4.1 Conversion of the cycloaddition *tert*-butyl methyl acrylate adduct (13d and 14d) to methyl acrylate adducts (13c and 14c)

A mixture of *tert*-butyl methyl acrylate adducts **13d** and **14d** (50.0 mg, 0.153 mmol) in a mixture of 5:1 methanol/HCl (1 cm^3) was stirred at 20°C for 6 h. After removal of the methanol the residual liquid was taken up into CH_2Cl_2 (15 cm^3) and washed with 5% K_2CO_3 (5 cm^3). The organic layer was dried (Na_2SO_4) and concentrated to give a mixture of methyl acrylate adduct **13c** and **14c** as a colorless liquid. The NMR spectrum as analyzed before for the CO_2Me singlets in toluene d_8 revealed the isomer **13c** and **14c** in a ratio of 56:44, respectively. The NMR spectrum revealed the absence of t-butyl proton thereby implying the complete ester exchange with methanol.

5.3.5 Cycloaddition of nitrone 7 to allyl alcohol (10e)

To a solution of the hydroxylamine **151** (140 mg, 0.91 mmol) in toluene (15 cm^3) was added paraformaldehyde (60 mg, 2.0 mmol) and the mixture was stirred using a magnetic stir bar at 65°C for 2 h. Thereafter, $MgSO_4$ (150 mg) was added followed by allyl alcohol **10e** (400 mg, 6.9 mmol). The reaction mixture was stirred in a closed vessel at 85°C for 6 h under N_2. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using ether/methanol (95:5) as eluent to give a non separable mixture of the cycloadducts **13e** and **14e** (168 mg, 83%) as a colorless liquid. Major and

minor isomers were found to be in a ratio of 62:38 as determined by integration of non overlapping proton signals at δ2.08 (1H, m), 2.31 (1H, m) for the major , and at δ2.14 (2H, m) for the minor isomer.

5.4 Cycloaddition of nitrone 7 to 1,1-disubstituted alkenes

5.4.1 Cycloaddition of nitrone 7 to methyl methacrolein (11a)

To a solution of the hydroxylamine **151** (77 mg, 0.5 mmol) in $CHCl_3$ (5 cm^3) was added paraformaldehyde (60 mg, 2 mmol) and the mixture was stirred under N_2 using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ (100 mg) was added followed by methyl metacrolein (140 mg, 2 mmol). The reaction mixture was then stirred under N_2 in a closed vessel at 50°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using 1:1 ether/hexane as eluent to give the hemiacetal **15a'** (40 mg, 34%) as colorless needles. m.p 156.2-156.3 °C; $\nu_{max.}$ (KBr) 3122, 2997, 2968, 2932, 2900, 2876, 2843, 1604, 1494, 1452, 1375, 1311, 1289, 1185, 1153, 1100, 1034, 996, 940, 878, 760 and 712 cm^{-1}; aldehyde absorption was not observed; δ_H($CDCl_3$, +20°C) 1.39 (3H, s), 1.86 (1H, ddd, *J* 2.8, 9.0, 12.0 Hz), 2.67 (1H, dt *J* 12.4, 8.7 Hz), 3.06 (1H, d, *J* 4.3 Hz, OH, exchangeable), 3.27 (1H, ddd, *J* 2.90, 8.85, 11.4 Hz), 3.60 (1H, dt, *J* 11.1, 8.9 Hz), 3.80 (2H, m), 3.91 (1H, dd, *J* 5.2, 9.8 Hz), 4.69 (1H, d, *J* 4.3 Hz), and 7.30 (5H, m); on D_2O exchange the signal at 3.06 disappeared while the signal at 4.69 collapsed into a siglet. The spectra revealed the presence of a trace amount of aldehyde by displaying signal at δ9.62 ppm. The spectra also revealed the presence of minor hemiacetal by displaying signal of the methyl proton as a singlet at 1.41

ppm. The ratio of the two hemiacetal was found to be 90:10, however, after D_2O exchange the ratio was changed to 64:36; δ_C($CDCl_3$, +20°C) 21.66, 32.38, 58.67, 68.06, 74.72, 89.46, 100.89, 126.97 (2C), 129.28, 128.44 (2C), 140.60; signals for the minor hemiacetal were also observed while the carbonyl carbon was absent (TMS: 0.0; $CDCl_3$ middle carbon:77.1).

The non overlapping signals of the minor hemiacetal were as follows : 1.41 (3H, s), 2.02 (1H, dd, *J* 8.1, 11.8 Hz), 2.55 (1H, m), 3.01 (1H, d *J* 7.05 Hz, OH exchangeable), 3.19 (1H, m), 3.45 (1H, m), 4.07 (2H, m), 4.37 (1H, dd, *J* 10.6, 13.4 Hz), 4.91 (1H, d, *J* 7.05 Hz);

The above reaction was repeated and the crude reaction product in methanol (3 cm^3) was reduced with $NaBH_4$ (100 mg) at room temperature (15 min). After removal of the solvent, the residue was taken up in water (10 cm^3), basified with K_2CO_3 and extracted with CH_2Cl_2 (3 x 15 cm^3). The organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography using CH_2Cl_2/methanol (97:3) as eluent to give the corresponding non separable mixtures of alcohol **15d** and **16d** as a colorless liquid (110 mg, 93%) in a ratio of 66:34, respectively, as determined by the integration of the non overlapping signals at δ1.83 ppm (1H, major isomer) and at δ1.93 ppm (1H, minor isomer). The stereochemistry was confirmed by comparison to the spectra of pure alcohol **15d** and **16d** obtained by LAH reduction of the pure **15b** and **16b**, respectively (*vide infra*).

5.4.2 Cycloaddition of nitrone 7 to methyl methacrylate (11b)

To a solution of the hydroxylamine **151** (460 mg, 3.0 mmol) in $CHCl_3$ (15 cm^3) was added paraformaldehyde (100 mg, 3.3 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h under N_2. Thereafter, $MgSO_4$ was added followed by methyl methacrylate (1.0 cm^3). The reaction mixture was stirred in a closed vessel at 50°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using 1:1 ether/hexane as eluent to give the cycloadduct **16b** (70 mg, 8.8%). Continued elution afforded a mixture of **15b** and **16b** (34 mg, 4.3%) and finally the isomer **15b** (532 mg, 66.8%) as a colorless liquid. The total isolated yield for the addition reaction was thus found to be 79.9%. The diastereomeric ratio of **15b** and **16b** was found to be around 86:14, respectively.

Major **15b**: $\nu_{max.}$ (neat) 3497, 2952, 2850, 1732, 1602, 1493, 1452, 1373, 1285, 1205, 1144, 983, 919, 848, 761 and 703 cm^{-1}; δ_H($CDCl_3$, +20°C) 1.52 (3H, s), 2.04 (1H, m), 2.73 (1H, m), 2.90 (1H, m and 1H OH underneath), 3.50 (1H, m), 3.65 (1H, m), 3.80 (3H, s), 3.95 (1H, m), 4.18 (1H, m) and 7.30 (5H, m); δ_H($CDCl_3$, -40°C) 1.51 (0.5x3H, s), 1.60 (0.5x3H, s), 2.00 (0.5x1H, m), 2.23 (0.5x1H, m), 2.41 (0.5x1H, m), 2.75 (1H, m), 2.97 (1H, m), 3.21 (0.5x1H, m), 3.73 (1H, m), 3.82 (0.5x3H, s), 3.86 (0.5x3H, s), 3.97 (0.5x1H, m), 4.10 (1H, m), 4.25 (0.5x1H, m and 1H, m) and 7.33 (5H, m); δ_C($CDCl_3$, -30°C) spectrum reveals the presence of two invertomers in a 1:1 ratio:

δ_C($CDCl_3$, -30°C): [22.53 and 24.36] (1C), [37.77 and 39.32] (1C), [49.07 and 52.80] (1C), [53.12 and 53.17] (1C), [63.75 and 68.45] (1C), [68.45 and 72.91] (1C), [80.26 and

83.89] (1C), [127.67 and 128.08] (1C), 128.15 (2C), [128.76 and 129.76] (2C), [135.22 and 138.13] (1C), [174.76 and 176.60] (1C).

Minor **16b**: $\nu_{max.}$ (neat) 3494, 2953, 2847, 1737,1494, 1452, 1407, 1372, 1286, 1199, 1125, 1063, 979, 933, 842, 761 and 703 cm^{-1}; $\delta_H(CDCl_3, +20°C)$ 1.55 (3H, s), 2.03 (1H, m), 2.50 (1H, m), 2.74 (1H, m), 2.93 (1H, m), 3.50 (1H, br, OH), 3.74 (1H, m), 3.81 (3H, s), 3.88 (1H, m), 3.99 (1H, m) and 7.30 (5H, m); $\delta_H(CDCl_3, -40°C)$ 1.59 (3H, s), 2.10 (1H, m), 2.52 (1H, m), 2.73 (1H, m), 2.95 (1H, m), 3.77 (1H, m), 3.84 (3H, s), 3.88 (1H, m and 1H OH underneath), 4.04 (1H, m) and 7.33 (5H, m); $\delta_C(CDCl_3, -30°C)$ 23.2, 29.7, 30.1, 38.5, 52.8, 53.4, 67.1, 71.6, 81.9, 127.9 (2C), 128.0, 128.5 (2C), 138.2, 175.9 (TMS: 0.0; $CDCl_3$ middle carbon:77.1) The NMR signals were sharp even at room temperature and the spectrum did not revealed the presence of any minor invertomer.

The above cycloaddition reaction was repeated at 0° and 25°C using the hydroxylamine **151** (100 mg, 0.65 mmol). In each case, the relative proportion of the other reactants was similar to the one carried out at 50°C. After the nitrone was made, $MgSO_4$ was added and the nitrone solution was brought to the required temperatures i.e 0° and 25°C after which the appropriate amount of methyl methacrylate was added. The reactions at 0° and 25°C were carried out for duration of 6 and 3 days, respectively. Usual work up as above and flash chromatography using 20:1 CH_2Cl_2/methanol mixture afforded the isomers at 0° and 25°C in 53 and 87% yields, respectively. Integration of several proton signals in ^1H NMR spectrum in $CDCl_3$ indicated the ratio of the isomers. The ratios were similar both in the crude reaction mixture and the isolated products. The

ratio of the **15b** and **16b** isomers at 0° and 25°C were found to be 90 : 10 and 87 : 13, respectively.

5.4.2.1 Cycloreversion of the cycloadduct 15f and trapping of the nitrone 7 by methyl methacrylate (11b)

A solution of **15f** (25 mg) and methyl metacrylate (300 mg) in toluene (5 cm^3) was thermolyzed in a closed vessel under N_2 at 95°C for 24 h. After removal of the solvent and the alkenes, the residual liquid was analyzed by ^1H NMR which revealed the presence of **15b** and **16b** in a ratio of 80:20, respectively. The NMR spectrum also revealed the presence of a minor amount of the starting adducts (~25%).

Similar cylcloreversion was carried out with acetyl derivative **158** and the ratio was found to be 80 : 20 for **161b** and **162b**, respectively.

5.4.2.2 Lithium aluminium hydride reduction of 15b and 16b to 15d and 16d

To a solution of **15b** (110 mg, 0.41 mmol) in ether (15 cm^3) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. Reaction was completed within 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture were added water (0.10 g), 10% NaOH solution (0.10 g) and water (0.40 g). The mixture was stirred at room temperature for 1 hour and then decanted and the residue was washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified with chromatography using CH_2Cl_2/methanol (97:3) as eluent to give **15d** (90 mg, 93 %) as a colorless liquid.

15d : $\nu_{max.}$ (neat) 3380, 3060, 3030, 2973, 2932, 2876, 1603, 1493, 1452, 1374, 1309, 1269, 1061, 893, 760, 735 and 703 cm^{-1}; δ_H($CDCl_3$, +20°C) 1.26 (3H, broad s), 1.83 (1H, m), 2.40 (1H, m), 2.60-3.30 (4H, broad) 3.52 (1H, m), 3.61 (1H, m), 3.71 (1H, m), 3.92(1H, m), 4.09 (1H, m), 7.30 (5H, m); δ_C($CDCl_3$, +20°C) 23.99, 35.07, 54.04, 79.28, 68.71, 72.15, 85.00, 128.08(3C), 128.63(2C), 138.10 (TMS: 0.0; $CDCl_3$ middle carbon: 77.00)

The above procedure was repeated with **16b** (50 mg) to give the corresponding **16d** (40 mg, 90 %) as a colorless liquid.

16d : $\nu_{max.}$ (neat) 3381, 3064, 3031, 2973, 2931, 2876, 1494, 1453, 1376, 1116, 1060, 889, 841, 760 and 703 cm^{-1}; δ_H($CDCl_3$, +20°C) 1.32 (3H, s), 1.66 (1H, m), 1.93 (1H, m), 2.38 (1H, m), 2.56 (1H, m), 3.00 (2H, m), 3.20-3.80 (4H, broad), 4.09 (1H, m), 7.30 (5H, m). δ_C($CDCl_3$, +20°C) 22.78, 35.76, 55.47, 68.35, 71.20, 74.43, 83.01, 127.88, 128.31(2C), 128.77(2C), 138.10 (TMS: 0.0; $CDCl_3$ middle carbon:77.00)

5.4.3 Cycloaddition of nitrone 7 with *t*-butyl methyl methacrylate (11c)

Cylcoaddition reaction was carried out under similar condition as above except that 0.5 mmol hydroxylamine **151** and 1 mmol t-butyl methyl metacrylate were used at 65°C for 6 h. Chromatography purification using ether/hexane as eluent gave the non separable adducts as a colorless liquid in 85% yield. The NMR spectrum of the crude as well as the purified mixture revealed the presence of 2 isomers. C(5) methyl proton appeared as

singlet at δ1.49 (major) and δ1.50 (minor) ppm while the t-butyl proton appeared at δ1.52 (major) and δ1.53 (minor) ppm in a ratio of 87:13, respectively. The major isomer was assigned to the stereochemistry of **15c** because of its similarity to major adduct **15b** in ^{1}H NMR spectral data.

$\nu_{max.}$ (neat) 3466, 3062, 3030, 2978, 2935, 2876, 1728, 1454, 1369, 1290, 1143, 1063, 931, 846, 758 and 702 cm^{-1}.

Major isomer **15c** displayed the following signals : δ_H($CDCl_3$, +20°C) 1.49 (3H, s), 1.52 (9H, s), 2.01 (1H, m), 2.68 (1H, m), 2.92 (2H, m), 3.73 (1H, dd, *J* 3.50, 11.45 Hz), 3.94 (1H, dd, *J* 5.05, 8.40 Hz), 4.18 (1H, dd, *J* 8.1, 11.45), 4.18 (1H, m) and 7.30 (5H, m);

5.4.4 Cycloaddition of nitrone 7 with methallylalcohol (11d)

To a solution of the hydroxylamine **151** (77 mg, 0.5 mmol) in toluene (5 cm^3) was added paraformaldehyde (60 mg, 2 mmol) and the mixture was stirred using a magnetic stir bar at 65°C for 2 h under N_2. Thereafter, $MgSO_4$ was added followed by methalyl alcohol **11d** (0.7 g). The reaction mixture was stirred in a closed vessel at 95°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using CH_2Cl_2/methanol (97:3) as eluent to give a non separable mixtures of alcohol **15d** and **16d** as a colorless liquid (97 mg, 82 %) in a ratio of 67:33 as determined by integration of C(5) methyl singlets. The ^{1}H spectrum of the mixture of **15d** and **16d** was compared with that of the pure isomer prepared before (*vide supra*).

5.4.4.1 DC reaction of methylallyl alcohol (11d) with nitrone 7 in the presence of $MgBr_2$

To a solution of the hydroxylamine **151** (77 mg, 0.5 mmol) in dichloromethane (10 cm^3), was added paraformaldehyde (17 mg, 0.56 mmol) and the mixture was stirred in a closed vessel under N_2 using a magnetic stir bar at 60°C for 2 h. Thereafter, the solution was cooled to room temperature and the volume of the solution was reduced to 3 cm^3 by gently blowing N_2 at 40°C. This process would remove moisture (H_2O) by evaporation along with CH_2Cl_2. Then $MgBr_2$ (92 mg, 0.5 mmol) was added to the solution. The resulting suspension was stirred at 20°C for 15 min after which methylallyl alcohol (40 mg, 0.55 mmol) was added. The reaction mixture was then stirred at 65°C in the closed vessel under N_2 for 24 h. During the reaction, a precipitate of magnesium salts was observed. After the elapsed time, the rection mixture was cooled to room temperature and was taken up in 5% K_2CO_3 (10 cm^3) and extracted with CH_2Cl_2 (3x15 cm^3). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography using CH_2Cl_2/MeOH (95:5) mixture ass eluent to give a non separable mixture of alcohols **15d** and **16d** as a colorless liquid (110 mg, 95%)**.** The ^1H NMR spectrum revealed the presence of **15d** and **16d** in a ratio of 97:3, respectively. The ratio was determined by integration of the C(5)-methyl singlets as before.

5.4.5 Cycloaddition of nitrone 7 with 11e

To a solution of the hydroxylamine **151** (77 mg, 0.5 mmol) in toluene (5 cm^3) was added paraformaldehyde (60 mg, 2 mmol) and the mixture was stirred using a magnetic stir bar

at 65°C for 2 h. Thereafter, $MgSO_4$ was added followed by alkene **11e** (0.7 g, 3.76 mmol). The reaction mixture was stirred in a closed vessel at 95°C for 6 h under N_2. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using ether as eluent to give a non separable mixtures of cycloadducts **15e** and **16e** as a colorless liquid (130 mg, 74 %) in a ratio of 60:40, respectively.

The following NMR signals were assigned to the major isomer **15e:**

0.09 (6H, s), 0.89 (9H, s), 1.33 (3H, s), 1.80 (1H, m), 2.22 (1H, m), 2.69 (1H, m), 2.98 (1H, m), 3.35 (1H, m), 3.55 (2H, m), 3.70 (1H, m), 3.81 (1H, m), 4.06 (1H, m), 7.32 (5H, m);

The following non overlapping NMR signals were assigned to the minor isomer **16e:**

16e : 0.077 (3H, s), 0.088(3H, s), 0.91 (9H, s), 1.39 (3H, s), 1.80 (1H, m), 2.06 (1H, m), 2.55 (1H, m), 2.85 (1H, m), 3.25-3.80 (4H, br), 4.04 (1H, m), 7.32 (5H, m);

To the above non separable mixture of adduct (50 mg, 0.14 mmol) in methanol (2 cm^3), was added a drop of concentrated HCl and the reaction mixture was stirred at room temperature for 30 minutes. After removal of the solvent, the reaction mixture was taken in water (5 cm^3), basified with K_2CO_3, and extracted with CH_2Cl_2 (3 x 10 cm^3). The organic layer was dried (Na_2SO_4), concentrated to give the mixture of alcohol **15d** and **16d** as a colorless liquid (30 mg, 90%) in a ratio of 58:42 as determined by the integration of the non overlapping signals at δ1.83 ppm (1H, major isomer) and δ1.93 ppm (1H, minor isomer).

5.4.6 Cycloaddition of nitrone 7 with dimethyl methylenemalonate (11f)

To a solution of the hydroxylamine **151** (617 mg, 4.03 mmol) in $CHCl_3$ (15 cm^3), was added paraformaldehyde (191 mg, 6.3 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ was added followed by dimethyl methylenemalonate (0.674 g 4.7 mmol). The reaction mixture was stirred in a closed vessel at 50°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using ether/hexane as eluent to give adduct **15f** (1.12 g, 89.8 %); $\nu_{max.}$: 3491, 3030,2956, 2885, 1746, 1453, 1436, 1285, 1204, 1110, 761 and 704 cm^{-1}; δ_H($CDCl_3$, +20°C) 2.70-3.20 (4H, broad, m), 3.70-4.20 (4H broad, m, including OH), 3.83 (3H, s), 3.84 (3H, s), 7.30 (5H, m); δ_C($CDCl_3$, +20°C) 36.24, 53.33, 53.46, 66.93, 72.30, 85.37, 91.18, 128.28, 128.69 (2C), 128.93 (2C), 138.18, 168.60, 169.14 (TMS : 0.0; $CDCl_3$ middle carbon: 77.07).

5.5 Cycloaddition of nitrone 7 with 1,2-disubstituted alkenes

5.5.1 Cycloaddition of nitrone 7 with *trans*-methyl crotonate (12a)

To a solution of the hydroxylamine **151** (154 mg, 1.00 mmol) in toluene (5.0 cm^3) was added paraformaldehyde (45 mg, 1.5 mmol) and anhydrous sodium sulphate (200 mg). The mixture was heated at 60°C for 1 h after which trans methyl crotonate **12a** (1.5 cm^3) was added and the reaction mixture was heated at 80°C under nitrogen in a closed vessel for 6 h. Removal of the solvent followed by silica gel chromatography using CH_2Cl_2 as eluent gave a non separable mixture of **17a**, **18a**, and **19a** as a colorless liquid. Continued elution gave a mixture of all four isomers followed by a pure sample of **20a** as a colorless

liquid. The combined yield of the cycloadducts was found to be 78%. Careful ^{1}H NMR analysis of the crude and the separated fraction revealed the ratio of the isomers **17a-20a** as 57:9:16:18, respectively. The NMR spectra in toluene-d_8 at 20°C was helpful in the determination of composition. In this solvent, the C(5)-methyl protons of **17a** and **18a**, and C(4)-methyl of **19a** and **20a** appeared at 1.13 (d, J 6.1), 1.16 (d, J 6.1), 0.83 (d, J 7.0), 0.78 (d, J 6.8), while the corresponding CO_2Me peak appeared as singlet at 3.25, 3.21, 3.32, 3.33 ppm, respectively.

The non separable mixtures of isomers **17a-19a** has the following IR absoptions : $\nu_{max.}$ (neat) 3453, 3030, 2954, 1739, 1603, 1494, 1453, 1380, 1204, 1062, 912, 846, 761,and 703 cm^{-1}.

The following signals were attributed to the major isomer **17a** from ^{1}H and ^{13}C spectra of the non separable mixture of isomers **17a-19a** :

Major isomer **17a** : Most of the signals were broad $\delta_H(CDCl_3, +20°C)$ $CDCl_3$ 1.41(3H, d, *J* 6.2 Hz), 2.75-3.50(4H, m), 3.71(3H, s), 3.7-4.1 (3 H, m), 4.54 (1H, m) 7.30 (5H, m). The C(5)-methyl of **18a** and C(4)-methyl of **19a** appeared at 1.44 (d, J 6.1 Hz) and 1.22 (d, J, 6.8 Hz), respectively, while the corresponding CO_2Me singlet appeared at 3.69 and 3.80 ppm, respectively. The broad signal at 4.54 ppm became a distinct quintet at 4.66 ppm (J 6.1 Hz) at -40°C while the corresponding signal for the minor isomer **18a** appeared at 4.30 ppm (quintet, J 6.2 Hz). However, the presence of invertomer can not be ascertained. The spectrum revealed the C(5)-H of the isomer **19a** as a doublet at δ4.12 ppm (J 5.3 Hz).

Major isomer **17a** δ_C($CDCl_3$, -40°C) 19.4, 52.6, 53.6, 56.5, 68.1, 70.1, 76.3, 128.1(2C), 128.7, 128.7(2C), 137.5, 172.8 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

Compound **20a :** δ_H($CDCl_3$, +20°C) 1.20 (3H, d, J 6.6 Hz), 2.60 (1H, br), 2.83 (1H, m), 3.06 (1H, m), 3.46 (1H, m), 3.78 (1H, m), 3.82 (3H, s), 3.95-4.20 (3H, m), 7,32 (5H, m).

The above reaction was repeated using 0.50 mmol of hydroxylamine **151** in toluene (5 cm^3). The resultant nitrone solution was concentrated to a volume of 3 cm^3 by blowing a gentle stream of N_2 at 60°C. This was done to ensure the removal of moisture. To then nitrone solution was added 0.5 mmol of $BF_3.OEt_2$ and the reaction mixture was heated at 80°C for 12 hours. Similar experiments were carried out in the presence of 0.5 mmol each of $ZnCl_2$ and $Ti(O^iPr)_4$. After removal of the solvent, the reaction mixture was taken in water (5 cm^3), basified with K_2CO_3, and extracted with CH_2Cl_2 (3 x 10 cm^3). The organic layer was dried (Na_2SO_4), concentrated and purified by silica gel chromatograpy using CH_2Cl_2/methanol 97:3 as eluent to give a non separable mixture of **17a-20a** as a colorless liquid in 50-65 % yield. The ratio of isomer **17a-20a** was found to be 59:13:13:15, respectively for reaction catalyzed by $BF_3.OEt_2$ and with $ZnCl_2$ the ratio was 58:14:11:17, respectively as analyzed before. Similar ratio for the reaction in the presence of $BF_3.OEt_2$ in $CHCl_3$ (58:11:14:17) was found. No reaction occurred in toluene in the presence of $Ti(O^iPr)_4$, therefore, the reaction was repeated in $CHCl_3$ to give **17a-20a** in a ratio 57:12:13:18.

5.5.1.1 Conversion of the cycloadducts 17a-20a to 17d-20d by reduction with $LiAlH_4$

A mixture of cycloadducts **17a-20a** in a known ratio of 58:14:11:17 was reduced as before with $LiAlH_4$ and the resultant non separable mixture of alcohols (colorless liquid: 95% yield) was analyzed by ^1H NMR ($CDCl_3$, +20°C) spectroscopy which revealed the presence of the C(5)-methyl protons of **17d** and **18d**, and C(4)-methyl of **19d** and **20d** at δ1.35 (br, overlapping), 1.36 (d, J 6.1), 1.09 (d, J 6.8), 1.06 (d, J 6.4), ppm, respectively, in an almost similar ratio of ~58:14:11:17 as determined by peak heights of the signals. Approximate description of the spectrum is as follows: δ_H($CDCl_3$, +20°C) 1.00-1.40 (3H, four doublets), 1.60-3.40 (5H, m), 3.60-4.10 (6H, m), 7.32 (5H, m).

5.5.2 Cycloaddition of nitrone 7 with *t*-butyl -methyl crotonate (12b)

To a solution of the hydroxylamine **151** (154 mg, 1.00 mmol) in toluene (3.0 cm^3) was added paraformaldehyde (45 mg, 1.5 mmol) and anhydrous sodium sulphate (200 mg). The mixture was heated at 60°C for 1 h after which *t*-butyl methyl crotonate (**12b)** (0.385 g, 1.25 mmol) was added and the reaction mixture was heated at 85°C under nitrogen in a closed vessel for 6 h. Removal of the solvent followed by purification over silica gel chromatography using hexane/ether as eluent gave a mixture of four isomers (252 mg, 82 %). ^1H NMR analysis of the crude and purified samples gave similar composition. The chromatography was not intended to separate the isomers, which has very similar R_f values (TLC/Silica, 1:1 hexane/ether).

The methyl signals of **17b, 18b, 19b, 20b,** in toluene d_8 appeared as doublets at 1.22 (*J* 6.40 Hz) 1.19 (*J* 6.10 Hz), 0.89 (*J* 6.70 Hz), 0.85 (*J* 6.70 Hz) ppm, respectively in a ratio of 53:9:16:22, respectively.

The low field methyl signals were attributed to C(4)-methyl since it is further away from the ring oxygen in compare to C(5)-methyls.

5.5.2.1 Conversion of *t*-butyl crotonate adducts 17b-20b to methyl crotonate adducts 17a - 20a

The mixture of *t*-butyl crotonate adduct (50.0 mg, 0.162 mmol) in methanol/HCl (5:1) was stirred at 20°C for 6 h. After removal of the methanol, the residual liquid was taken up into CH_2Cl_2 (15 cm^3) and washed with 5% K_2CO_3 (5 cm^3). The organic layer was dried (Na_2SO_4) and concentrated to give methyl crotonate adduct as a colorless liquid (41 mg, 95 %). The NMR spectrum as analyzed before for the CO_2Me singlets revealed the isomers **17a, 18a, 20a, 19a** in a ratio of 58:10:10:22, respectively. The NMR spectra revealed the absence of t-butyl proton thereby implying complete ester exchange with methanol.

5.5.3 Cycloaddition of nitrone 7 with crotonaldehyde (12c) and conversion of the cycloadducts 17c-20c to 17d-20d by reduction with $NaBH_4$

To a solution of the hydroxylamine **151** (75 mg, 0.5 mmol) in toluene (3.0 cm^3) was added paraformaldehyde (45 mg, 1.5 mmol) and anhydrous sodium sulphate (200 mg). The mixture was heated at 65 °C for 2 h after which crotonaldehyde **12c** (300 mg, 4.2 mmol) was added and the reaction mixture was heated at 85°C under nitrogen in a closed vessel for 6 h. After removal of the solvent, the residual mixture of cycloadducts **17c-20c** upon reduction with $NaBH_4$, as described before, followed by chromatography using CH_2Cl_2/methanol 95:5 as eluent gave a non separable mixture of diols **17d-20d** as a colorless liquid (106 mg, 90 %). The spectrum was analyzed as before to reveal the presence of the diols **17d-20d** in a ratio of 32:26: 23:19, respectively.

5.5.4 Cycloaddition of nitrone 7 with crotyl alcohol (12d)

To a solution of the hydroxylamine **151** (75 mg, 0.5 mmol) in toluene (3.0 cm^3) was added paraformaldehyde (60 mg, 2.0 mmol) and anhydrous sodium sulphate (200 mg). The mixture was heated at 65 °C for 2 h after which crotyl alcohol **12d** (300 mg, 4.1 mmol) was added, and the reaction mixture was heated at 85°C under nitrogen in a closed vessel for 6 h. After removal of the solvent, the residual mixture of cycloadducts **17d-20d** followed by chromatography using CH_2Cl_2/methanol 95:5 as eluent gave a non separable mixture of diols **17d-20d** as a colorless liquid (103 mg, 89 %). The spectrum of the

mixtures was analyzed as before to reveal the presence of the diols **17d-20d** in a ratio of 38:7:10:45, respectively.

5.5.4.1 DC reaction of crotyl alcohol (12d) with nitrone 7 in the presence of $MgBr_2$

The reaction was repeated as described before except that crotyl alcohol (**12d**) (40 mg, 0.55 mmol) instead of methylallyl alcohol (**11d**) was used. Similar work up and chromatographic purification afforded a non separable mixture of alcohols **19d-20d** as a coluourless liquid (111 mg, 96%)**.** The ^{1}H NMR spectrum revealed the presence of **19d** and **20d** in a ratio of 91:9, respectively. The ratio was determined by integration of the C(5)-methyl singlets as before.

5.5.5 Cycloaddition of nitrone 7 with *trans*-methyl γ–hydroxycrotonate (12e)

To a solution of the hydroxylamine **151** (75 mg, 0.5 mmol) in toluene (3.0 cm^3) was added paraformaldehyde (25 mg, 0.83 mmol) and anhydrous sodium sulphate (200 mg). The mixture was heated at 65°C for 2 h after which *trans*-methyl γ–hydroxycrotonate **12e** (116 mg, 1.0 mmol) was added and the reaction mixture was heated at 85°C under nitrogen in a closed vessel for 16 h. After removal of the solvent, the residual mixture of cycloadducts **17e-20e** followed by chromatography using CH_2Cl_2/methanol 95:5 as eluent gave a non separable mixture of adducts **17e-20e** as a colorless liquid (112 mg, 79 %) in a ratio of 50:13:30:7, respectively, as determined by ^{1}H NMR integration or peak height of the CO_2Me singlets which appeared at δ3.70 (for **18e**), 3.72 (for **17e**), 3.82 (for

19e), and 3.88 (for **20e**). The down field singlets were attributed to the C(5)-CO_2Me of **19e** and **20e** while the upfield singlets were assigned to the C(4)-CO_2Me of **17e** and **18e**. Approximate description of the spectrum is as follows: δ_H($CDCl_3$, +20°C) 1.70-2.30 (2H, broad), 2.50-3.50 (5H, m), 3.60-4.60 (9H, m including the CO_2Me singlets), 7.32 (5H, m).

5.5.5.1 DC reaction of *trans*-methyl γ–hydroxycrotonate (12e) with nitrone 7 in the presence of $MgBr_2$

The reaction was repeated as described before except that *trans*-methyl γ–hydroxycrotonate (**12e**) (62 mg, 0.53 mmol) instead of methylallyl alcohol (**11d**) was used. Similar work up and chromatographic purification afforded a non separable mixture of alcohols **17e** and **18e** as a colourless liquid (107 mg, 76%)**.** The ^{1}H NMR spectrum revealed the presence of **17e** and **18e** in a ratio of 19:81, respectively. The ratio was determined by integration of the C(5)-methyl singlets as before. The NMR spectra of the crude as well as purified mixture failed to detect the presence of regioisomers **19e** and **20e**. The C(5)H of the isomers **17e** and **18e** appeared at δ4.59 and 4.37, respectively as broad signals due to nitrogen inversion.

Approximate description of the spectrum is as follows: δ_H($CDCl_3$, +20°C) 2.50-3.50 (5H, m), 3.60-4.10 (5H, m), 3.70 (3H, s), 4.37 (1H, m), 7.32 (5H, m).

5.5.6 Cycloaddition of nitrone 7 with methyl cinnamate (12f)

To a solution of the hydroxylamine **151** (154 mg, 1.00 mmol) in toluene (3.0 cm^3) was added paraformaldehyde (45 mg, 1.5 mmol) and anhydrous sodium sulphate (200 mg).

The mixture was heated at 60 °C for 1 h after which methyl cinnamate **12f** (0.203 g, 1.25 mmol) was added and the reaction mixture was heated at 85°C under nitrogen in a closed vessel for 6 h. Removal of the solvent followed by purification over silica gel chromatography using hexane/ether as eluent gave a mixture of four isomers (277 mg, 84.7%). ^{1}H NMR analysis of the crude and purified samples gave similar composition.

The ^{1}H NMR spectrum in $CDCl_3$ revealed the presence of **17f-20f** as indicated by the presence of four methyl singlets at 3.73, 3.71, 3.82, 3.80, respectively. The phenyl group at C-5 was indicated by the presence of signals at 5.50 (major) and 5.30 (minor) which are assigned to the C5(H) in similar cases[85]. The spectrum in toluene-d_8 revealed the presence of the corresponding methyl singlets free of any overlapping signals at 3.24**,** 3.20, 3.32, 3.30 ppm in a ratio of 72:10:12:6, respectively. The downfield methyl singlets were attributed to the C-5-CO_2Me signals as a result of their proximity to the ring oxygen. As previously noted in nitrone-cinnamate cycloadditions[85], the major product is assigned with *endo* oriented CO_2Me. As a result of nitrogen inversion most of the signals were very broad indeed.

5.5.7 Cycloaddition of nitrone 7 with *t*-butyl cinnamate (12g)

The above nitrone-methyl cinnamate cycloadditon reaction was repeated using the same condition except that *tert*-butyl cinnamate (**12g**) (1.25 mmol) instead of methyl cinnamate (**12f**) was used. Removal of the solvent followed by purification over silica gel chromatography using hexane/ether as eluent gave a mixture of four isomers (314 mg, 85 %). ^{1}H NMR analysis of the crude and purified samples gave similar composition. The t-

butyl proton signals for **17g-20g** appeared in $CDCl_3$ at δ1.44, 1.43, 1.52, 1.47 ppm, respectively in a ratio of 76:7:12:5 and the streochemisty was correlated to the methyl cinnamate adducts by converting the former to the later as described below.

The t-butyl singlets were well separated and free of any competing signals. The C-5 H of **17g** appeared at 5.46 ppm (major) and that of **18g** at 5.30 (minor). As a result of nitrogen inversion most of the signals were very broad indeed.

5.5.7.1 Conversion of *t*-butyl cinnamate adducts 17g-20g to methyl cinnamate adducts 17f-20f

The mixture of *t*-butyl cinnamate adduct **17g-20g** in a ratio of 76:7:12:5 (50.0 mg, 0.153 mmol) in methanol/HCl (5:1) was stirred at 20°C for 6 h. After removal of methanol, the residual liquid was taken up into CH_2Cl_2 (15 cm^3) and washed with 5 % K_2CO_3 (5 cm^3). The organic layer was dried (Na_2SO_4) and concentrated to give methyl cinnamate adduct **17f- 20f** as a colorless liquid (48 mg, 97%). The NMR spectrum as analyzed before for the CO_2Me singlets revealed the isomer **17f- 20f** in a ratio of 78:7:10:5, respectively. The NMR spectra revealed the absence of t-butyl proton thereby implying complete ester exchange with methanol.

5.6 Cycloaddition of nitrone 7 with trisubstituted alkene

5.6.1 Cycloaddition of nitrone 7 with dimethyl mesaconate (163)

To a solution of the hydroxylamine **151** (140, 0.91 mmol) in toluene (5.0 cm^3), was added paraformaldehyde (50 mg, 1.67 mmol) and anhydrous sodium sulphate (200 mg). The

mixture was heated at 65°C for 2 h after which dimethyl mesonate (0.219 g, 1.38 mmol) was added and the reaction mixture was heated at 85 °C under nitrogen in a closed vessel for 24 h. Removal of the solvent followed by purification over silica gel chromatography using CH_2Cl_2/methanol 95:5 as eluent gave minor isomer **165** (50 mg, 19%) as a colorless liquid. Further elution gave major isomer **164** (174 mg, 67%) as a colorless liquid. The ratio of the major **164** and minor isomer **165** was found to be 80:20 as determined by integration of C(5)-methyl singlets. ^{1}H NMR failed to detect other regioisomers since no singlet was observed for C(5)-H. analysis of the crude and purified samples gave similar composition.

Major isomer **164 :**

$\nu_{max.}$(neat) 3466, 3060, 3030, 2990, 2953, 2875, 1740, 1494, 1453, 1437, 1376, 1238, 1206, 1115, 1062, 1030, 854, 736, and 703 cm^{-1}; δ_H($CDCl_3$, 20°C) 1.42 (3H, s), 1.66 (1H, m), 3.18(2H, m), 3.69(3H, s), 3.73(1H, m), 3.85(3H, s), 3.98(1H, t, *J* 8.40 Hz), 4.13(1H, t, *J* 9.63Hz), 7.32 (5H, m); δ_C($CDCl_3$, 20°C) 18.28, 52.34, 52.73, 53.15, 53.31, 63.86, 68.49, 81.97, 127.71, 128.21 (2C), 129.45 (2C), 134.70, 170.93, 175.26 (TMS : 0.0; $CDCl_3$ middle carbon: 77.00).

Minor isomer **165 :**

$\nu_{max.}$(neat) 3507, 3061, 3031, 2954, 2869, 1738, 1494, 1454, 1436, 1372, 1240, 1209, 1114, 1063, 1063, 850, 736, and 703 cm^{-1}; δ_H($CDCl_3$, 20°C) 1.45 (3H, s), 1.69 (1H, m), 2.92 (1H, t, *J* 9.00 Hz), 3.08 (1H, t, *J* 8.68 Hz), 3.28(1H, m), 3.73(3H, s), 3.81(1H, m), 3.86(3H, s), 3.90(1H, t, *J* 8.40 Hz), 4.02(1H, m), 7.32 (5H, m); δ_C($CDCl_3$, 20°C) 18.70,

52.13, 52.42, 53.04, 57.05, 66.90, 72.13, 83.61, 128.11, 128.21 (2C), 128.56 (2C), 137.91, 171.18, 174.53 (TMS : 0.0; $CDCl_3$ middle carbon: 77.00).

5.7 General procedure for the preparation of the acetyl derivatives of the cycloadducts.

A solution of the the cycloadduct (100 mg) and acetic anhydride (0.5 g) in $CHCl_3$ (2 cm^3) was heated in a closed vessel under N_2 at 70°C for 5 h. After removal of the solvent and excess acetic anhydride by a blowing a gentle stream of N_2, the residual liquid was taken up in ether (30 cm^3) and washed with 5% $NaHCO_3$ solution (10 cm^3). The organic layer was concentrated and chromatographed using a mixture of hexane/ether as eluant to afford the acetyl derivatives in above 75% yields.

The styrene-adducts **13a, 14a** was thus acetylated to give a non separable mixture of isomers to give a nonseparable mixture of isomers **159a** and **160a** as colorless liquid; $\nu_{max.}$(neat) 3030, 2959, 1724, 1494, 1454, 1382, 1366, 1241, 1046, 761 and 701 cm^{-1}; Approxinate description of the signals of the major and minor isomers is given below:

Major isomer (**159a)**: δ_H($CDCl_3$, 20°C) 1.95 (3H, s), 2.14 (1H, m), 2.68 (1H, m), 3.06 (2H, m), 4.05 (1H, m), 4.44 (1H, m), 4.69 (1H, m), 5.22 (1H, m), 7.40 (5H, m),

Minor isomer (**160a)**: δ_H($CDCl_3$, 20°C) 1.95 (3H, s), 2.14 (1H, m), 2.58 (1H, m), 3.06 (2H, m), 4.00 (1H, m), 4.40 (1H, m), 4.69 (1H, m), 5.09 (1H, m), 7.40 (5H, m)

Methyl acrylate-adduct 13c was acetylated to give the acetate derivative (**159c)** as colorless liquid; $\nu_{max.}$(neat) 3030, 2954, 2850, 1731, 1495, 1454, 1383, 1231, 1046, 833, 760,and 703 cm^{-1}; δ_H($CDCl_3$, +20°C) 1.95 (3H, s), 2.39 (1H, m), 2.54 (1H, m), 2.98 (1H, m), 3.76 (3H, s), 3.92 (1H, m), 4.36 (1H, m), 4.66 (2H, m), 7.31 (5H, m); δ_H($CDCl_3$, -30°C) 1.99 (3H, s), 2.42 (1H, m), 2.61 (1H, m), 2.74 (1H, m), 3.02(1H, m), 3.80 (3H, s), 3.90 (1H, m), 4.38(1H, m), 4.72 (1H, dd, *J* 3.95, 11.0 Hz), 4.79 (1H, dd, *J* 4.25, 9.75), 7.33 (5H, m); δ_C($CDCl_3$, -30°C) 21.10, 31.87, 52.10, 52.70, 66.50, 68.46, 75.07, 128.24(2C), 128.35, 128.61(2C), 137.77, 171.09, 172.45 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

Methyl acrylate-adduct 14c was acetylated to give the acetate derivative (**160c);** $\nu_{max.}$(neat) 3030, 2992, 2955, 2853, 1738, 1444, 1380, 1228, 1045, 915, 842, 759, 733 and 705 cm^{-1}; δ_H($CDCl_3$, +20°C) 1.95 (3H, s), 2.41 (1H, m), 2.50 (1H, m), 2.92 (1H, m), 3.78 (3H, s), 4.04 (1H, m), 4.37 (1H, m), 4.55 (2H, m), 7.31 (5H, m); δ_C($CDCl_3$, +20°C) 20.78, 32.72, 52.24, 52.57, 66.16, 69.52, 76.15, 128.08, 128.36(4C), 137.95, 170.56, 172.57 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

Methylmethacrylate-adduct 16b was acetylated to give acetate derivative **(162b)** as colorless liquid**;** $\nu_{max.}$ (neat) 3448, 3028, 2956, 2914, 2848, 1738, 1587, 1452, 1380, 1282, 1232, 1122, 1044, 762 and 701 cm^{-1}; δ_H($CDCl_3$, +20°C) 1.54 (3H, s), 1.93(3H, s), 2.03 (1H, m), 2.61 (1H, m), 2.75 (1H, m), 2.95 (1H, m), 3.76 (3H, s), 3.92 (1H, m), 4.35 (1H, dd, *J* 7.48 and 11.12 Hz), 4.67 (1H, m) and 7.29 (5H, m); δ_C($CDCl_3$, +20°C) 20.81,

23.99, 38.40, 52.41, 53.40, 66.53, 66.96, 82.43, 128.12, 128.38(2C), 128.40(2C), 138.14, 170.65, 174.86 (TMS: 0.0; $CDCl_3$ middle carbon:77.0)

Methylmethacrylate-adduct 15b was acetylated to give acetate derivative **(161b)** as colorless liquid**;** $\nu_{max.}$ (neat) 3030, 2986, 2954, 1742, 1453, 1379, 1234, 1145, 1048, 762 and 703 cm^{-1}; δ_H($CDCl_3$, +20°C) 1.49 (3H, s), 1.94(3H, s), 2.06 (1H, m), 2.76 (1H, m), 2.95 (2H, m), 3.79 (3H, s), 4.01 (1H, m), 4.38 (1H, dd, *J* 6.55 and 11.15 Hz), 4.58 (1H, m) and 7.31 (5H, m); δ_C($CDCl_3$, +20°C) 20.84, 23.91, 38.66, 52.45, 52.79, 66.23, 66.06, 82.92, 128.02, 128.31(2C), 128.50(2C), 138.00, 170.61, 174.88 (TMS: 0.0; $CDCl_3$ middle carbon:77.0)

Dimethyl methylenemalonate(DMMM)-adduct 15f was acetylated to give acetate derivative **158** as colorless liquid**;** $\nu_{max.}$ (neat) 3492, 3034, 3003, 2956, 2885, 2848, 1743, 1603, 1494, 1437, 1285, 1205, 1110, 1062, 917, 843, 761 and 704 cm^{-1}; δ_H($CDCl_3$, +20°C) 2.01 (3H, s), 2.60-3.20 (4H, broad m), 3.80 (3H, s), 3.85 (3H, s), 4.03 (1H, m), 4.42 (1H, dd, *J* 6.88 and 11.12 Hz), 4.66 (1H, m) and 7.31 (5H, m); δ_C($CDCl_3$, +20°C) 20.82, 36.20, 52.87, 53.22, 53.32, 66.15, 69.21, 85.88, 128.33, 128.45(2C), 128.54(2C), 137.70, 168.87, 169.28, 170.58 (TMS: 0.0; $CDCl_3$ middle carbon:77.1)

Under the reaction no acetyl derivative of **Camphor-DMMM-adduct** was obtained.

5.8 Cycloaddition of nitrone 8 with monosubstituted alkenes

5.8.1 Cycloaddition of nitrone 8 with styrene (10a)

To a solution of the hydroxylamine **157** (370 mg, 2.0 mmol) in $CHCl_3$ (15 cm^3) was added paraformaldehyde (72 mg, 2.4 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ was added followed by styrene (1.5 cm^3). The reaction mixture was stirred in a closed vessel at 65°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using 1:4 ether/hexane as eluent to give the non separable mixtures of the cycloadducts **22a** and **23a** (489 mg, 81 %) as colourless liquid. Major and minor isomer was found in a ratio of 96: 4 as determined by integration C5(H) signal. The C(5)-H signal of **22a** appeared at δ5.13 (major) and that of **23a** at δ5.01 (minor).

ν_{max} (neat) 3536, 3062, 3028, 2951, 1604, 1492, 1454, 1391, 1368, 1291, 1242, 1216, 1120, 1099, 1067, 1025, 990, 974, 943, 809, 760, and 700 cm^{-1}; δ_H($CDCl_3$, +20°C) 0.78(3H, s), 0.97 (3H, s), 1.06 (2H, m), 1.20 (3H,s), 1.47(1H, m), 1.75(2H, m), 2.36 (1H, m), 2.74(1H, m), 2.90(2H, m), 3.49(2H, m), 3.67(1H, m), 5.14(1H, m), 7.31(5H, m); δ_H($CDCl_3$, -40°C) 0.79(3H, s), 0.98 (3H, s), 1.08 (2H, m), 1.19 (3H,s), 1.48(1H, m), 1.75(2H, m), 2.39(1H, m), 2.82(1H, m), 2.90(2H, m), 3.50(1H, t, *J* 2.45 Hz), 3.67(2H, dd, *J* 2.45, 6.7 Hz), 5, 14(1H, m), 7.38(5H, m); δ_C($CDCl_3$, -30°C) 11.4, 21.1, 21.3, 27.2, 32.6, 37.9, 46.7, 49.0, 49.6, 54.2, 74.3, 78.2, 80.3, 125.8(2C), 127.4, 128.5(2C), 143.1 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

5.8.2 Cycloaddition of nitrone 8 with methyl acrylate (10c)

To a solution of the hydroxylamine **157** (741 mg, 4.0 mmol) in $CHCl_3$ (20 cm^3), was added paraformaldehyde (135 mg, 4.5 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ was added followed by methyl acrylate (1.5 cm^3). The reaction mixture was stirred in a closed vessel at 55°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using 1:4 ether/hexane as eluent to afford the major and minor cycloadducts **22c** and **23c** (962 mg, 85 %) as non separable mixture of isomers. Crystallizations from hexane/ether afforded major cycloadduct **22c** as colorless needles. The diastereomeric ratio of **22c** and **23c** was found to be around 65:35, respectively.

Major isomer **22c**

ν_{max} (KBr) 3506, 2952, 1742, 1444, 1362, 1221, 1080, and 813 cm^{-1}; δ_H($CDCl_3$, +20°C) 0.78(3H, s), 0.99 (3H, s), 1.07 (2H, m), 1.11 (3H,s), 1.46(1H, m), 1.72(2H, m), 2.51 (1H, m), 2.61(1H, m), 2.83(2H, d, *J* 6.7 Hz), 3.32(1H, m), 3.71(1H, d, *J* 6.4 Hz), 3.76(3H, s), 4.04(1H, OH), 4.56(1H, m); δ_H($CDCl_3$, -40°C) 0.77(3H, s), 1.00 (3H, s), 1.09 (2H, m), 1.18 (3H,s), 1.47(1H, m), 1.73(2H, m), 2.55 (1H, m), 2.71(1H, m), 2.88(2H, m), 3.36(1H, m), 3.75(1H, d, *J* 6.7 Hz), 3.80(3H, s), 4.22(1H, OH), 4.64(1H, m); δ_C($CDCl_3$, -30°C) 11.4, 21.0, 21.5, 27.3, 32.5, 32.7, 46.7, 49.2, 49.9, 52.3, 52.7, 73.67, 73.73, 80.4, 173.7 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

The following ^{1}H-NMR signals for the minor isomer **23c** was extracted from the spectrum of the mother liquor which was rich in the minor isomer **23c**: 0.78(3H, s), 0.96(3H, s), 1.12 (3H, s), 3.74(3H, s) and 4.53(1H, m).

5.8.3 Cycloaddition of nitrone 8 with 1-hexene (10f)

To a solution of the hydroxylamine **157** (186 mg, 1.0 mmol) in toluene (6 cm^3), was added paraformaldehyde (72 mg, 2.4 mmol) and the mixture was stirred using a magnetic stir bar at 65°C for 2 h. Thereafter, $MgSO_4$ was added followed by 1-hexene (1.5 cm^3). The reaction mixture was stirred in a closed vessel at 85°C for 8 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using 1:4 ether/hexane as eluent to give the non separable mixtures of the cycloadducts **22f** and **23f** (223 mg, 79 %) as colourless liquid in a ratio of 95:5 as determined by the peak height of major and minor methyl singlet of the champor moiety.

ν_{max} 3344, 2955, 2929, 2876, 1460, 1386, 1370, 1289, 1120, 1096, 1073 and 1005 ($CDCl_3$, +20°C) 0.78(3H, s), 0.89 (3H, t, *J* 7.0 Hz), 0.97 (3H, s), 1.17 (3H, s), 1.00-1.78 (11H, m), 1.91(1H, m), 2.34 (1H, m), 2.66 (1H, m), 2.76 (1H, m), 3.29 (1H, m), 3.59(1H, m), 3.64 (1H, m), 4.10 (1H, m);

Methyl singlet for the minor isomer were observed at 0.82, 0.99 and 1.09 ppm. The peak height of these were used to calculate the ratio of isomers as 95:5.

δ_C($CDCl_3$, 20°C) 11.32, 13.99, 21.20, 21.67, 22.56, 27.24, 28.44, 33.00, 34.63, 35.76, 46.74, 49.12, 49.97, 53.62, 74.38, 76.89, 80.65 (TMS : 0.0; $CDCl_3$ middle carbon: 77.01).

5.9 Cycloaddition of nitrone 8 with 1,1-disubstituted alkenes

5.9.1 Cycloaddition of nitrone 8 with methyl methacrylate (11b)

To a solution of the hydroxylamine **157** (370 mg, 2.0 mmol) in $CHCl_3$ (15 cm^3) was added paraformaldehyde (72 mg, 2.4 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter $MgSO_4$ was added followed by methyl methacrylate **11b** (1.5 cm^3). The reaction mixture was stirred in a closed vessel at 50°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using 1:4 ether/hexane as eluent to give the mixture of minor isomer (138 mg, 23.3 %) contaminated with small percentage of major isomer. Continued elution afforded the major isomer (383 mg, 64.5 %) contaminated by minor portion of minor isomer. Repeated chromatography was unable to separate the two isomers since they have very close R_f value. The total isolated yield for the addition reaction was thus found to be 87.8 %. The diastereomeric ratio of **24b** and **25b** was found to be around 66:34, respectively, as determined by integration of several methyl proton signals in ^{1}H-NMR spectrum of the crude reaction mixture.

Minor isomer 25b : $\nu_{max.}$ (neat) 3540, 2953, 2876, 1745, 1479, 1454, 1392, 1370, 1355, 1289, 1201, 1098, 985, 963, 829, and 753 cm^{-1}; δ_H($CDCl_3$, +20°C) 0.76(3H, s), 0.98(3H, s), 1.05(2H, m), 1.30(1H, m), 1.49(3H, s), 1.68(2H, m), 2.08(1H, ddd, *J* 1.85, 9.00, and 11.00 Hz), 2.60(1H, app q, *J* 8.85 Hz), 2.81(2H, m), 3.28(1H, t, *J* 8.1), 3.72 (1H, d, *J* 6.4 Hz), 3.75(3H, s).

Major isomer 24b : $\nu_{max.}$ (neat) 3547, 2952, 1736, 1458, 1391, 1369, 1291, 1201, 1121, 1074, 984, 828, and 750 cm^{-1} ; δ_H($CDCl_3$, +20°C) 0.78(3H, s), 0.96(3H, s), 1.60(2H, m),

1.17(3H, s), 1.46(1H, m), 1.53(3H, s), 1.70(2H, m), 2.22(1H, m), 2.82(3H, m), 3.31(2H, m), 3.67(1H, m), 3.75(3H,s); Low temperature NMR spectra revealed the presence of two invertomers in a ratio of 84 : 16. The spectra revealed the presence of complicated signals, however the following non-overlapping signal were extracted from the spectra :

Major invertomer of major isomer 24b: δ_H($CDCl_3$, +20°C) 0.78(3H, s), 0.97(3H, s), 1.16(3H,s), 1.57(3H, s), 3.79(3H, s). δ_C($CDCl_3$, -30°C) 11.4, 21.2, 21.5, 25.0, 27.0, 32.7, 39.9, 46.2, 49.0, 49.7, 52.9, 53.5, 73.8, 80.3, 81.7, 173.8 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

Minor invertomer of major isomer 24b: The corresponding proton NMR signals were at 0.81, 0.94, 1.19, 1.55, 3.75 respectively. δ_C($CDCl_3$, -30°C) 15.3, 20.3, 21.9, 22.9, 26.4, 38.4, 46.2, 47.9, 49.1, 52.5, 57.0, 66.0, 74.5, 80.4, 80.7, 175.7 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

5.9.2 Cycloaddition of nitrone 8 with dimethyl methylenemalonate

To a solution of the hydroxylamine **157** (556 mg, 3.00 mmol) in $CHCl_3$ (15 cm^3), was added paraformaldehyde (150 mg, 5.0 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ was added followed by dimethyl methylenemalonate (0.506 g, 3.51 mmol). The reaction mixture was stirred in a closed vessel at 50°C for 6 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using ether/hexane as eluent which then crystallized from hot ether to give adduct **24f** (805 mg, 78.7 %). Mp : 130.3-132.0 °C; $\nu_{max.}$ (KBr) 3515, 2958, 2881, 1753, 1440, 1290, 1270, 1216, 1095, 1003, 926, 828, and

771 cm^{-1}; δ_H($CDCl_3$, +20°C) 0.77 (3H, s), 0.97(3H, s), 1.07(2H, m), 1.10(3H, s), 1.45 (1H, m), 1.70(2H, m), 2.70 (1H, m), 2.86 (2H, m), 2.94(1H, m), 3.37(1H, m), 3.67(1H, m), 3.74(1H, m), 3.79(3H, s), 3.81(3H, s); δ_C($CDCl_3$, 20°C) 11.36, 21.11, 21.54, 27.39, 32.90, 36.90, 46.93, 49.30, 50.39, 53.26, 53.45, 53.51, 74.51, 80.63, 84.42, 167.15, 170.19 (TMS : 0.00; $CDCl_3$ middle carbon: 77.04).

5.10 Cycloaddition of nitrone 8 with *trans*-methyl crotonate (12a)

To a solution of the hydroxylamine **157** (370 mg, 2.0 mmol) in $CHCl_3$ (15 cm^3), was added paraformaldehyde (72 mg, 2.4 mmol) and the mixture was stirred using a magnetic stir bar at 45°C for 4 h. Thereafter, $MgSO_4$ was added followed by *trans*-methyl crotonate(1.5 cm^3). The reaction mixture was stirred in a closed vessel at 65°C for 12 h. The reaction mixture was filtered, concentrated and the residual liquid was chromatographed over silica using CH_2Cl_2/hexane as eluent to give a pure sample **26**. Continued elution give the mixture of **26** and **27**. Further elution with CH_2Cl_2 gave a mixture of **28** and **29** as well as a pure sample of **28** as a colorless liquid. The total isolated yield of all the isomers was found to be 77 %. The diastereomeric ratio of major **26** and minor isomer **27** was found to be around 95:5, respectively, as determined by integration of C5(H) signals at (-30°C) of the major and minor isomer at 4.48 ppm (quint) and 4.18 ppm (quint, *J* 6.4 Hz).

26 : ν_{max} (neat) 3542, 2953, 2879, 1740, 1438, 1391, 1371, 1290, 1202, 1095, 1075, and 817 cm^{-1}; δ_H($CDCl_3$, +20°C) 0.79 (3H, s), 0.96 (3H, s), 1.05 (2H, m), 1.16 (3H, s), 1.37 (3H, d, *J* 6.4 Hz), 1.47 (1H, m), 1.72 (2H, m), 2.60-3.70 (6H, bs), 3.73 (3H,s), 4.45 (1H,

m); δ_H($CDCl_3$, -30°C) 0.78 (3H,s), 0.97(3H,s), 1.06 (2H, m), 1.15 (3H, s), 1.40 (3H, d, *J* 6.1 Hz), 1.46 (1H, m), 1.73 (2H, m), 2.88 (1H, d, *J* 6.7 Hz), 3.00 (1H, t, *J* 9 Hz), 3.15 (1H, dt, *J* 4.9, 8.25 Hz), 3.44 (1H, d, *J* 2.15 Hz), 3.58 (1H, t, *J* 8.85 Hz), 3.65 (1H, dd, *J* 2.45, 7 Hz), 3.76 (3H, s), 4.48 (1H,m); δ_C($CDCl_3$,-30°C) 11.4, 21.4, 21.5, 22.1, 26.9, 32.7, 46.7, 49.0, 49.6, 52.6, 53.9, 56.5, 73.5, 75.5, 80.3, 172.7 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

28 : ν_{max} (neat) 3523, 2924, 2892, 1742, 1653, 1457, 1364, 1212 and 1093 cm^{-1}; δ_H($CDCl_3$, +20°C) 0.77 (3H, s), 0.98 (3H, s), 1.07 (2H, m), 1.16 (3H, s), 1.29 (3H, d, *J* 7.0 Hz), 1.44 (1H, m), 1.67-1.76 (3H, m), 2.23 (1H, m), 2.60-3.74 (4H, m), 3.76 (3H, s), 4.04 (1H, d, *J* 4.30 Hz); δ_C($CDCl_3$,-30°C) 11.43, 18.63, 21.05, 21.53, 27.28, 32.57, 42.24, 46.77, 49.14, 49.85, 52.52, 60.76, 73.63, 80.31, 80.82 (TMS : 0.0; $CDCl_3$ middle carbon: 77.1).

The NMR spectra of the mixtures of the compounds **28** and **29** revealed the presence of C(5)H at 4.14 (*J* 5.80 Hz) as doublets. Careful proton NMR analysis of the crude sample and the separated fraction revealed the presence of **28** and **29** in a ratio of 88:12, respectively. The regioisomeric ratio of (**26** + **27**) and (**28** + **29**) was found to be 67:33, respectively. The isomeric ratio for **26-29** was thus calculated to be 63.6:3.4:29:4, respectively.

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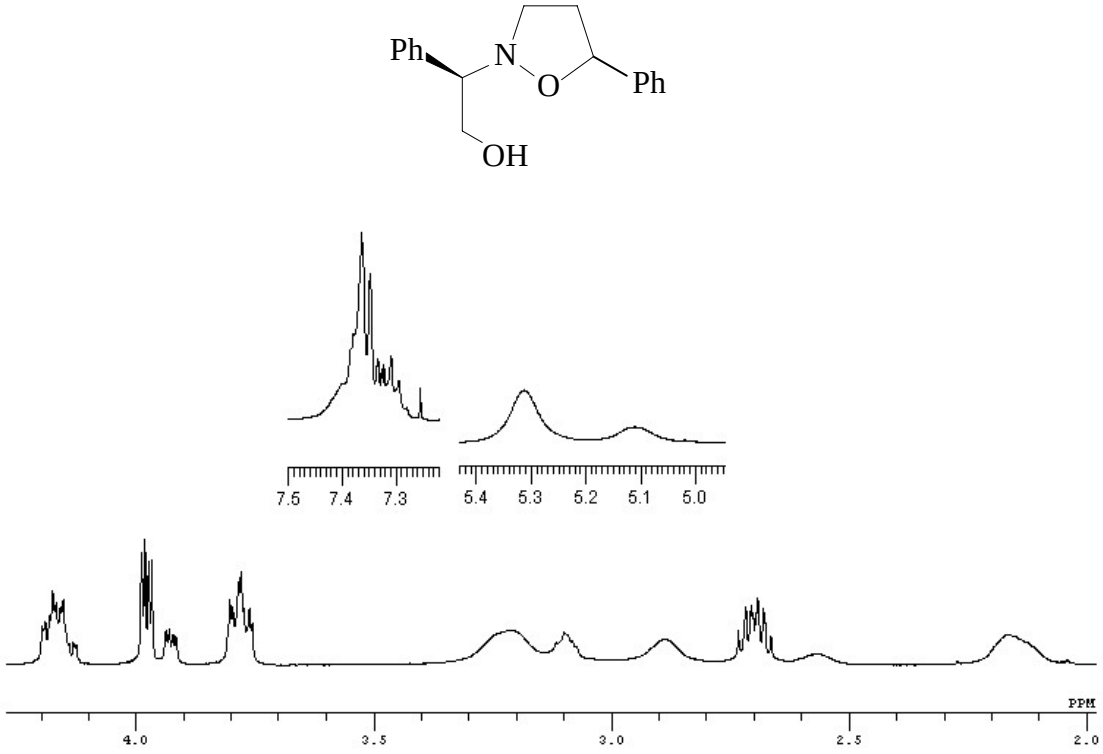
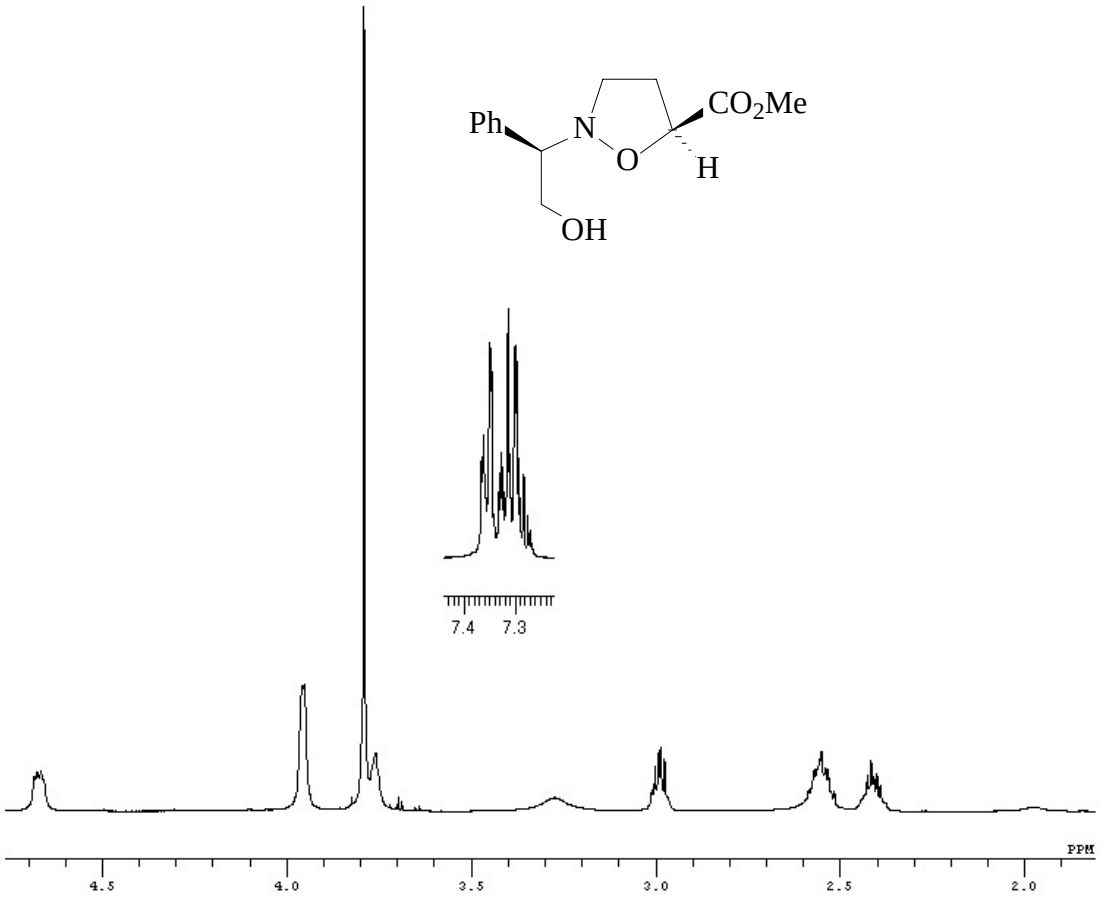
APPENDIX



^{1}H-NMR of **13,14a** in $CDCl_3$ at 20°C



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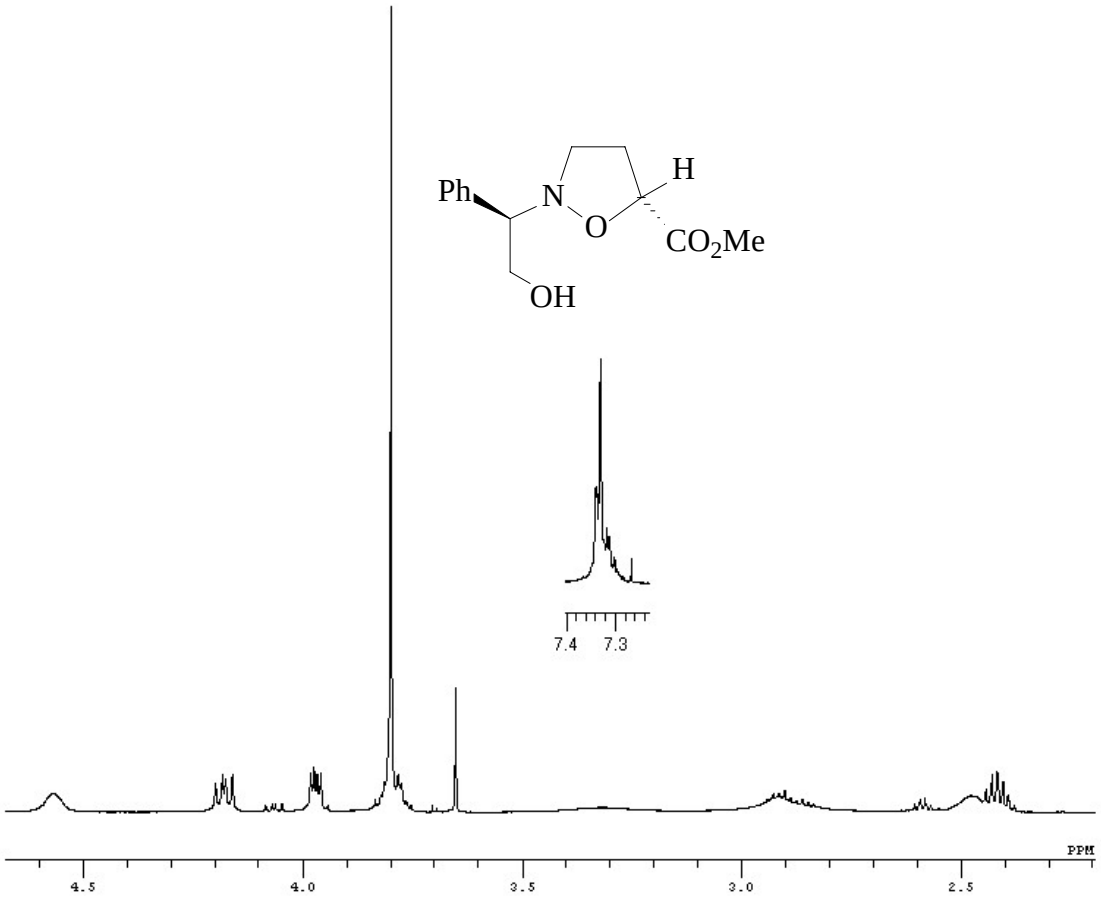
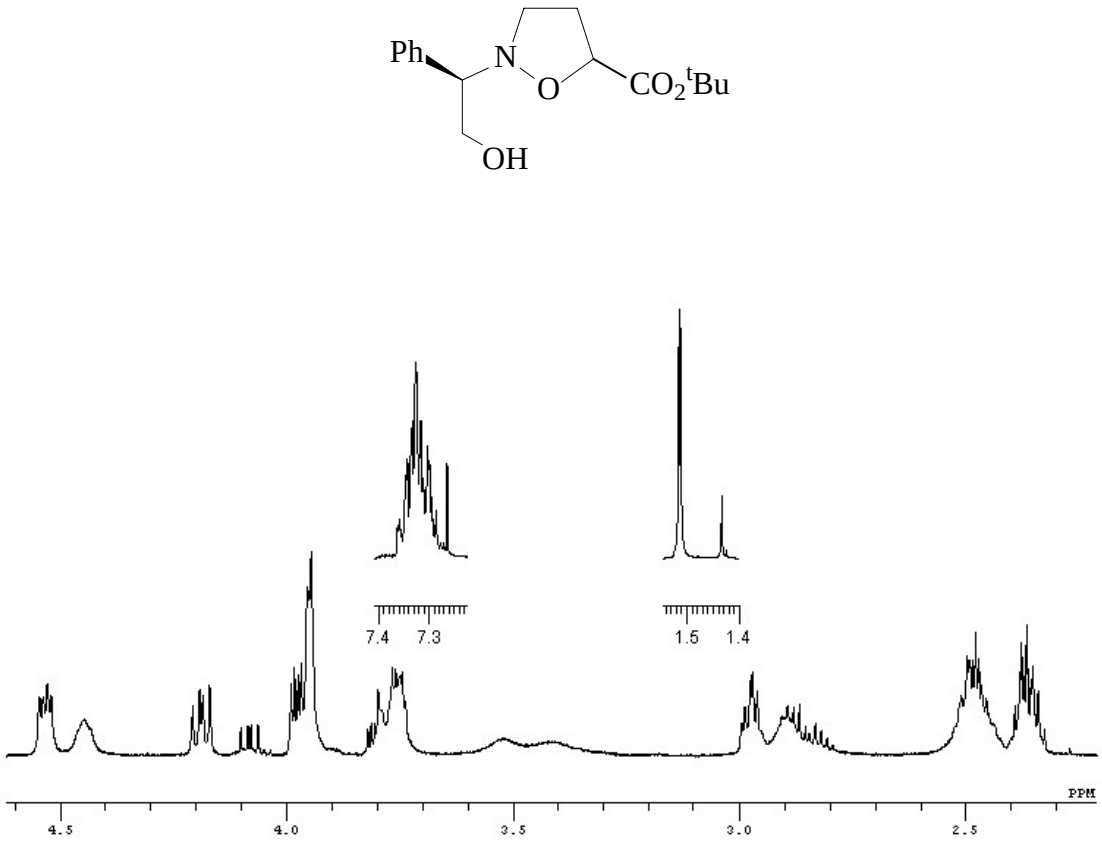


^{1}H-NMR of **14c** in $CDCl_3$ at 20°C



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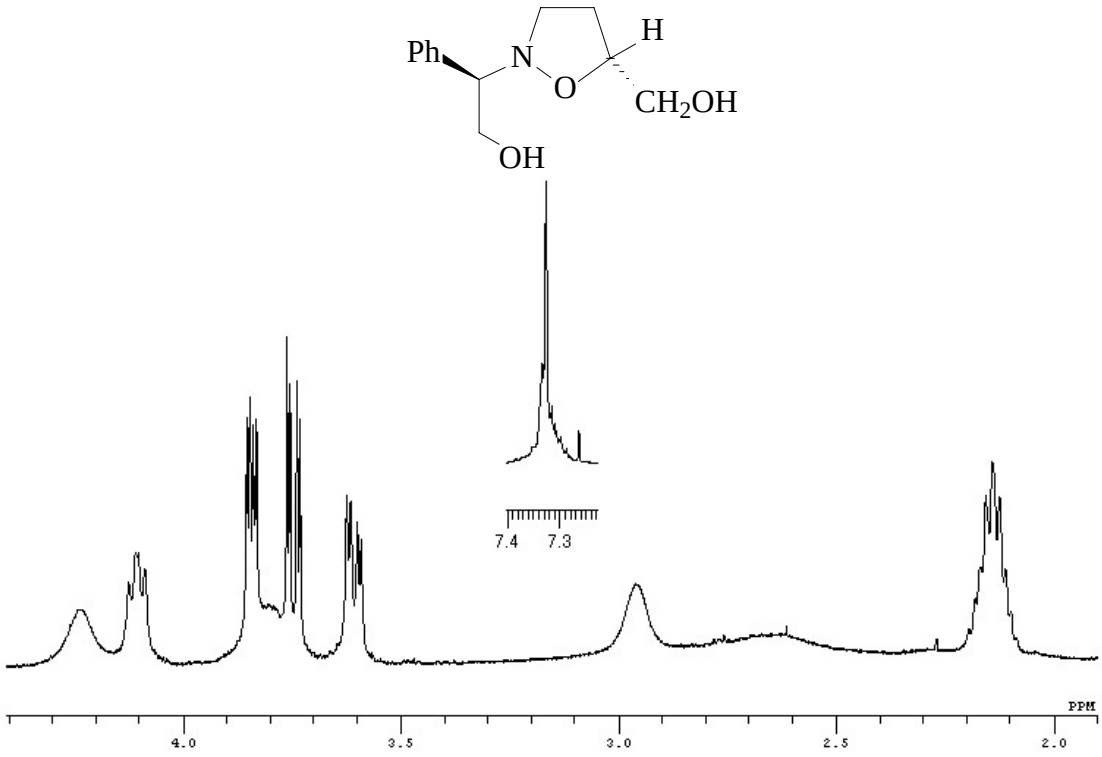

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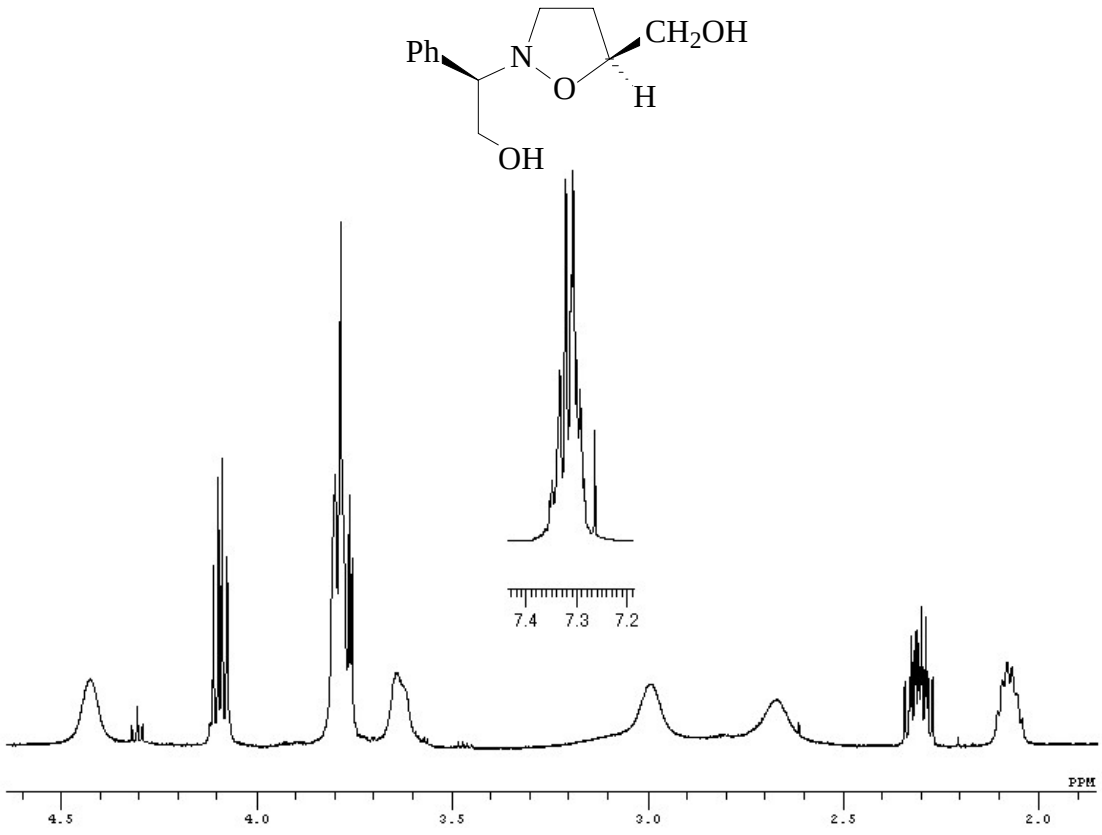

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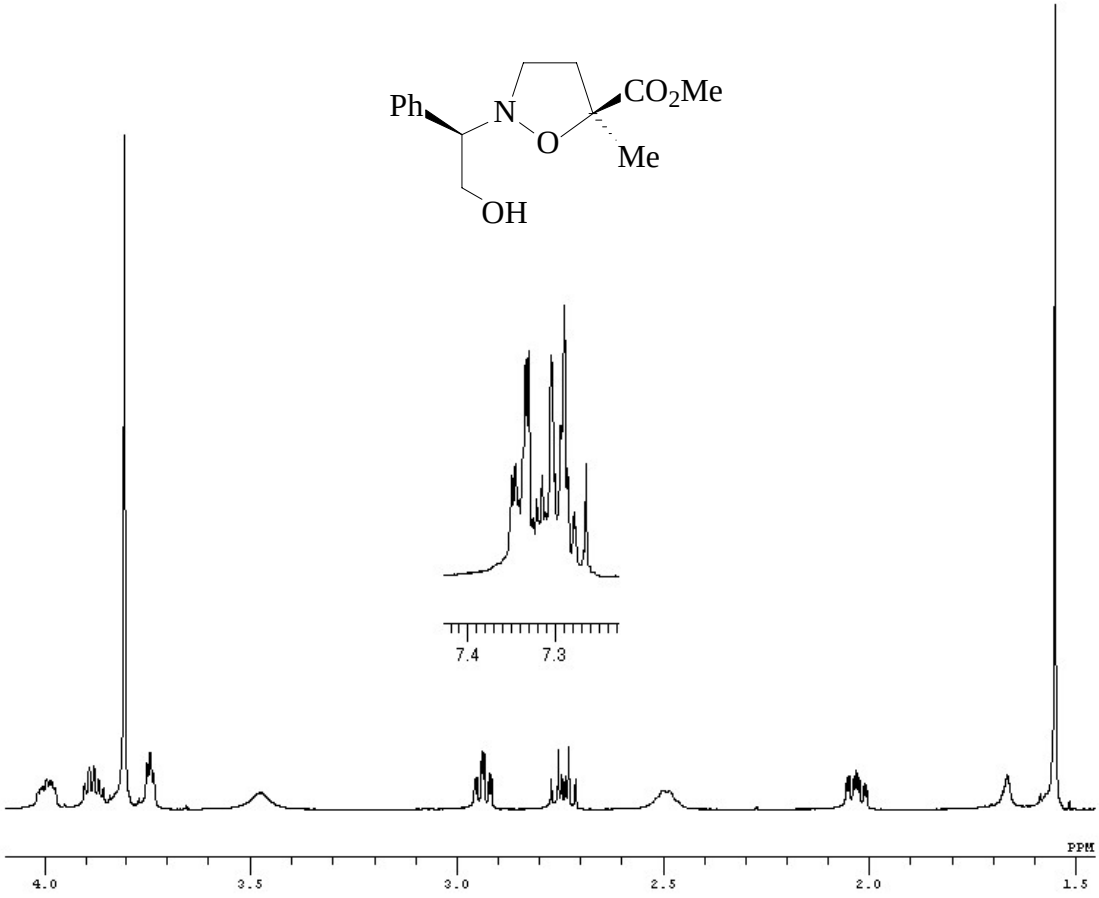
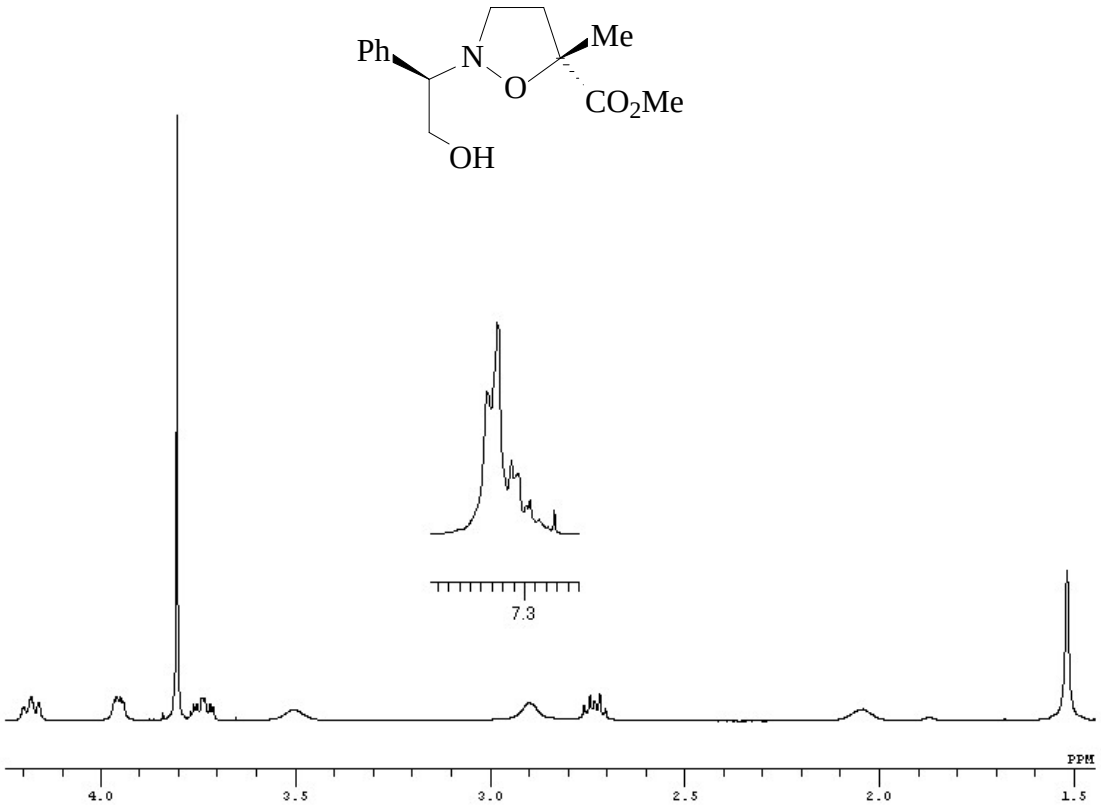


^{1}H-NMR of **16b** in $CDCl_3$ at 20°C



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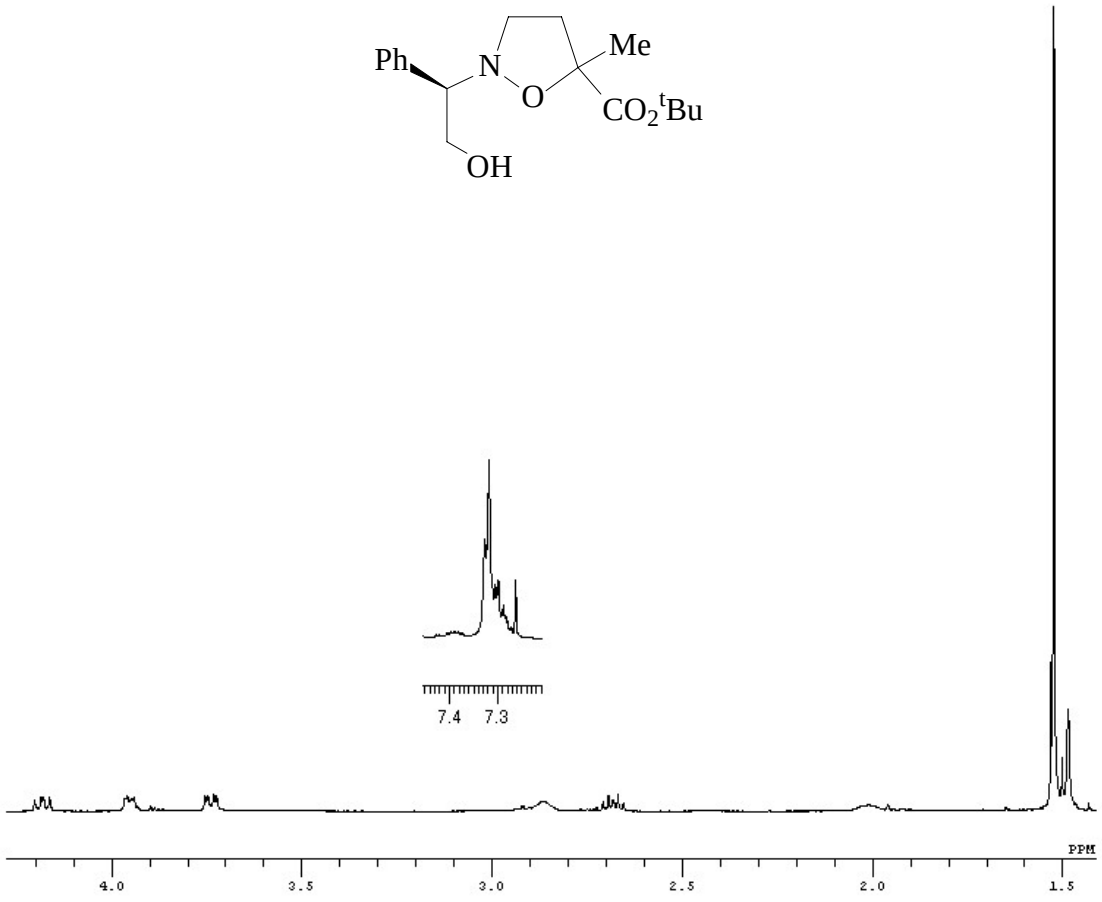
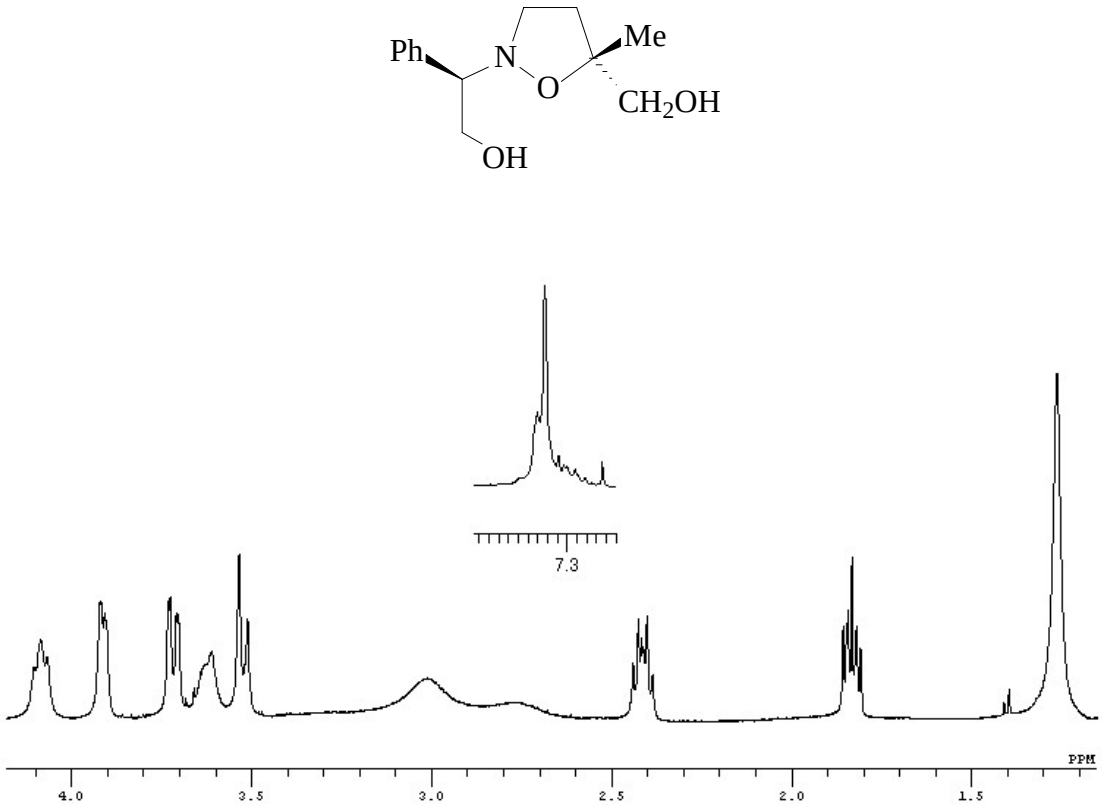


^{1}H-NMR of **15,16c** in $CDCl_3$ at 20°C



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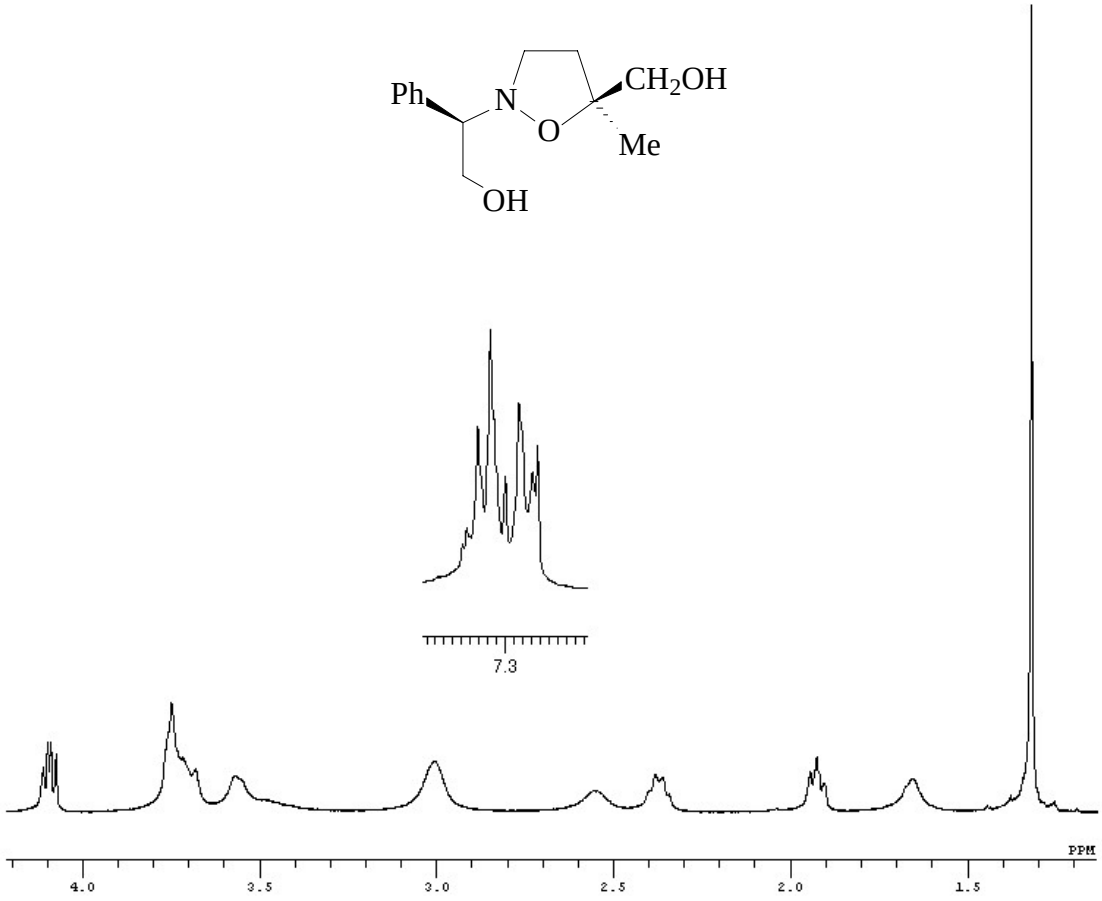

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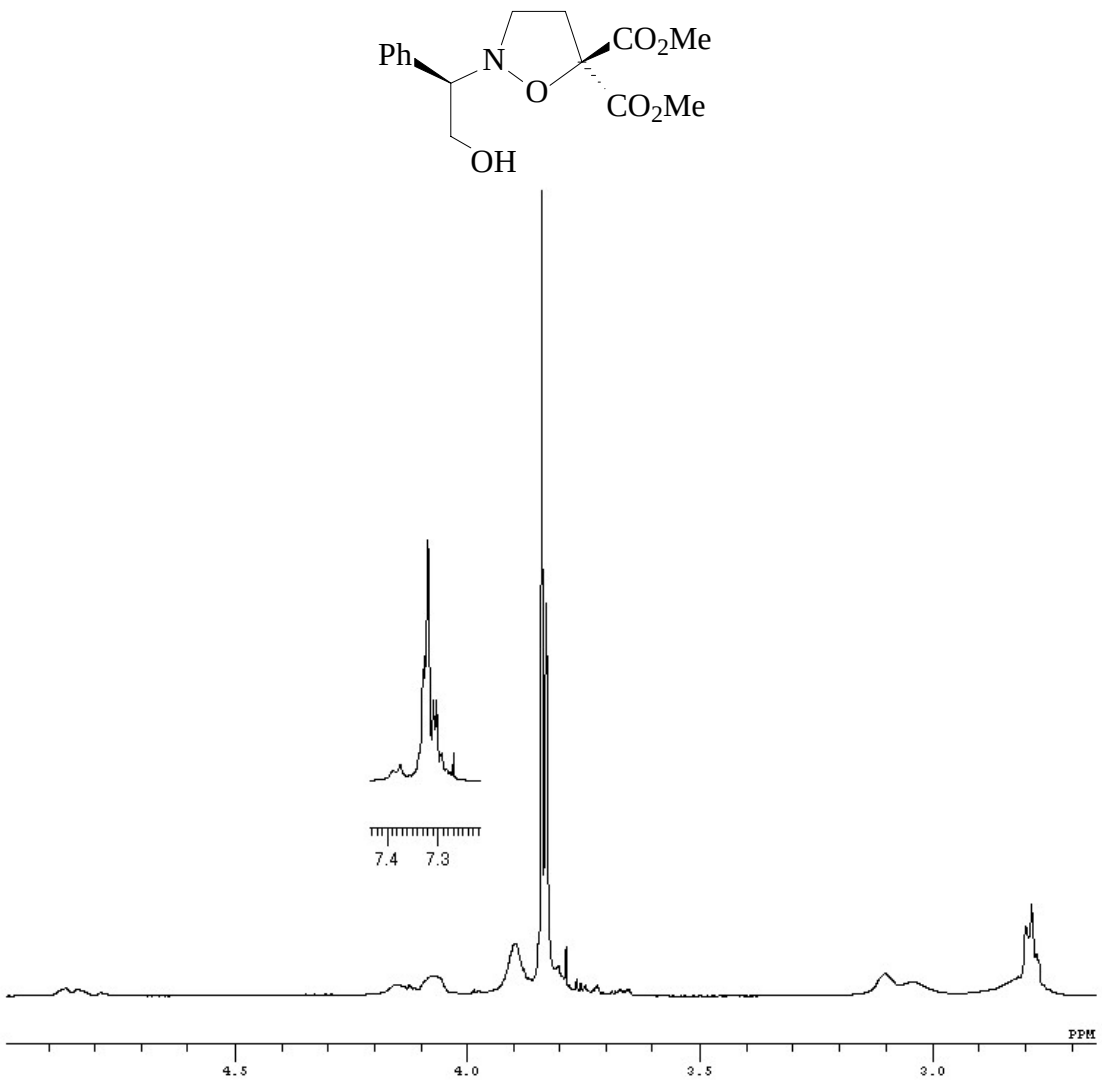

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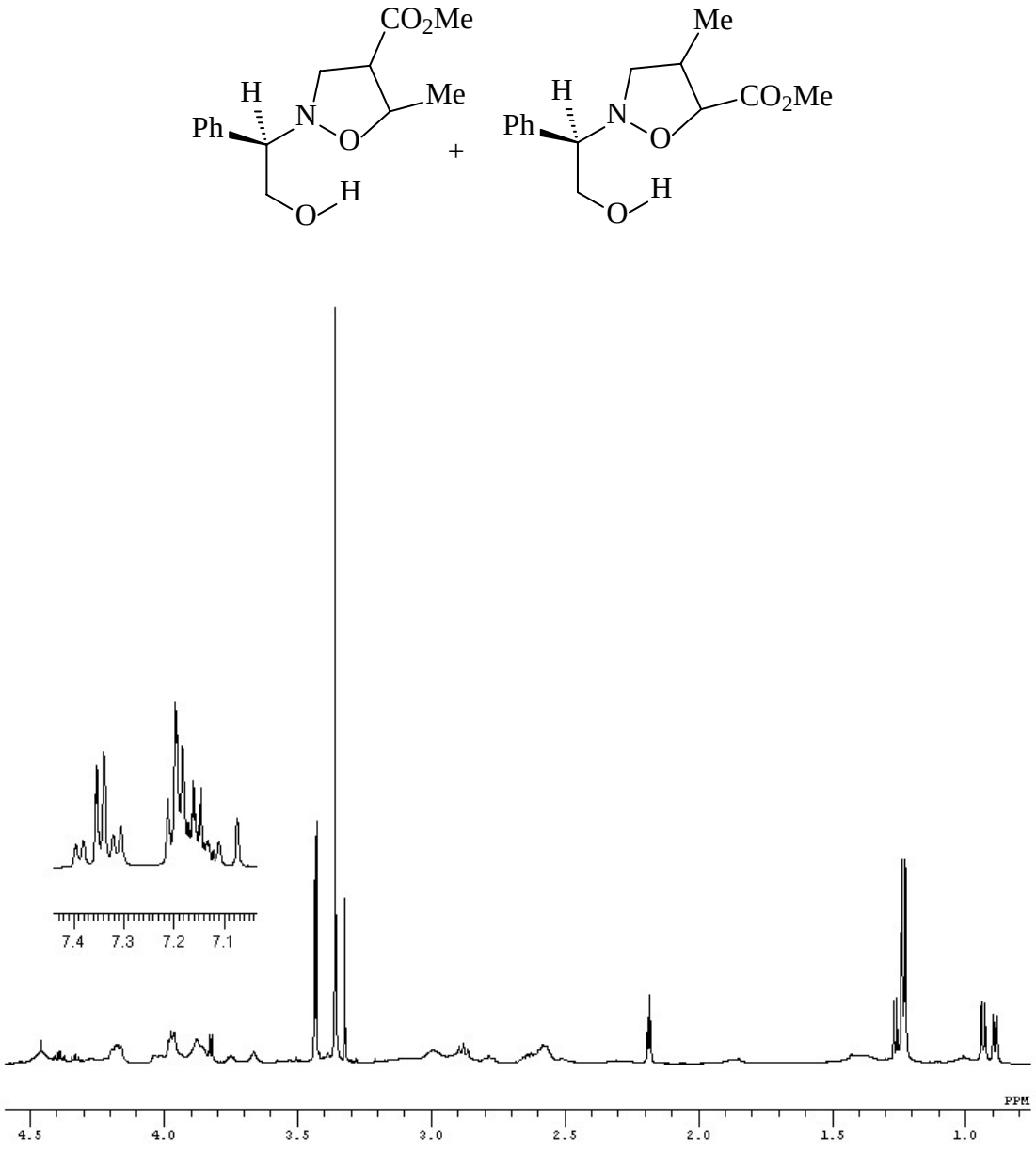
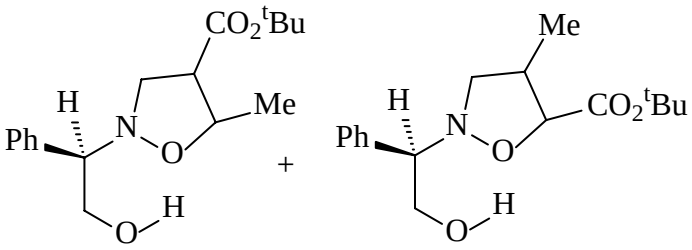
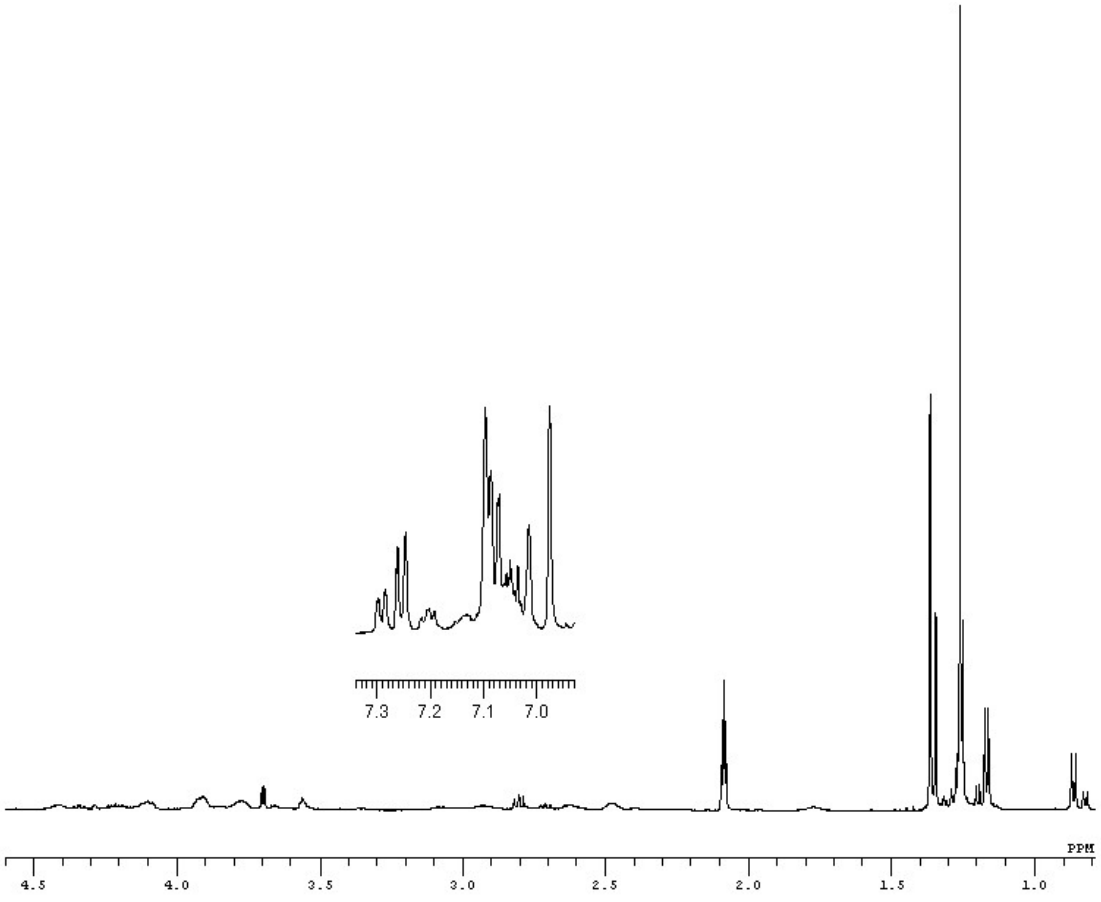


^{1}H-NMR of **17-20a** in toluene-d_8 at 20°C





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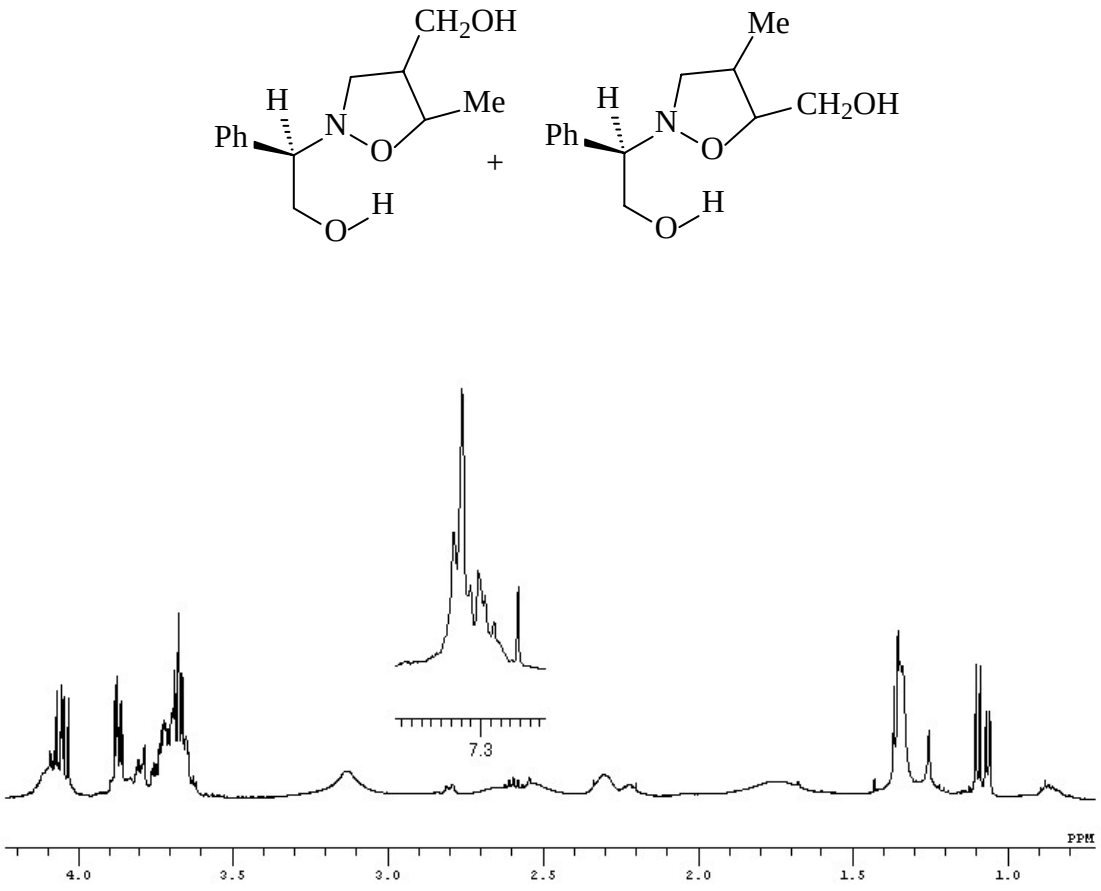
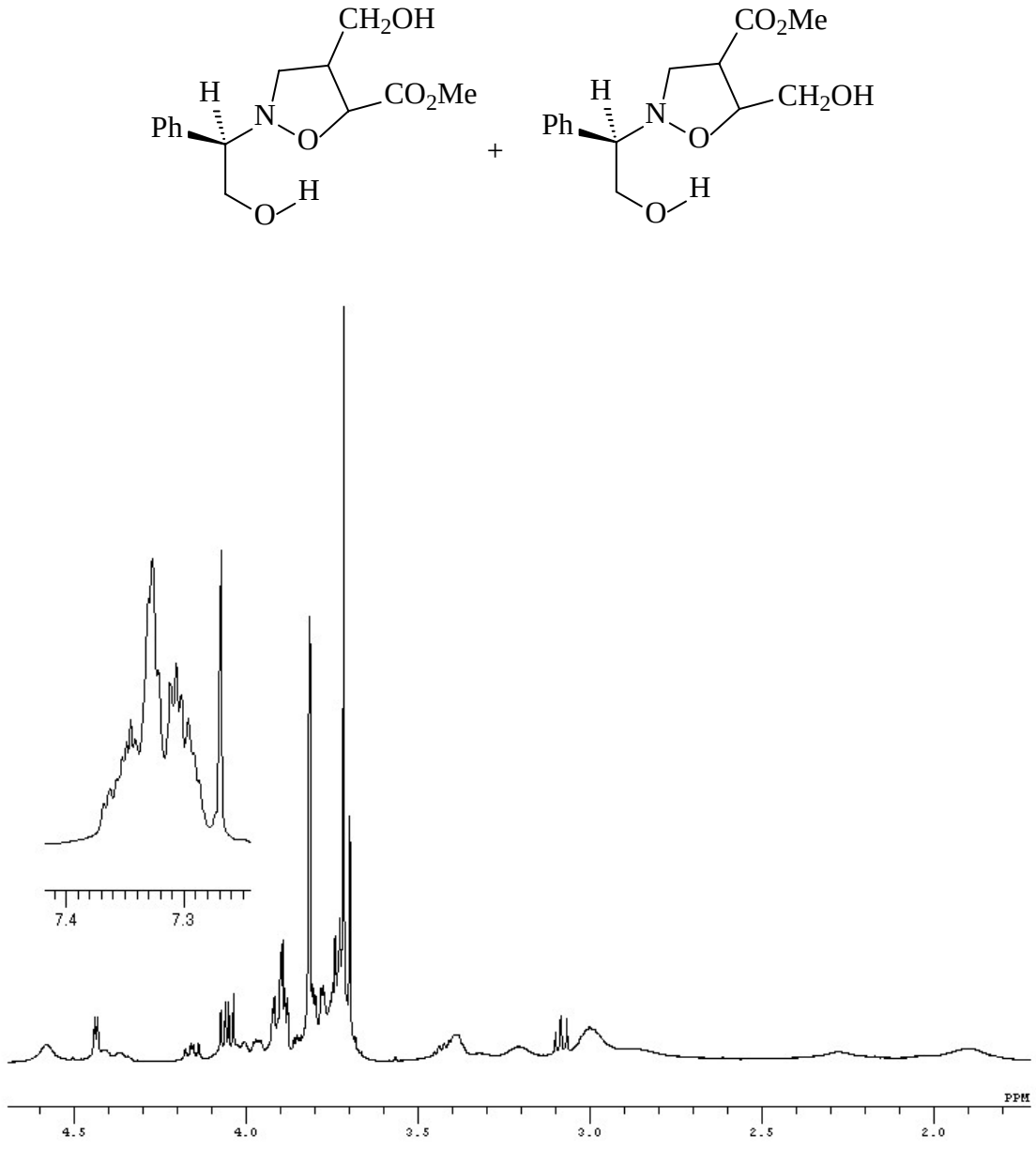
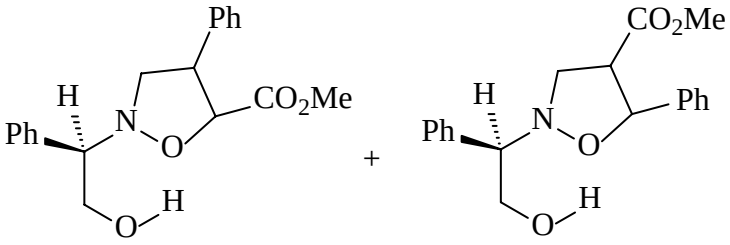
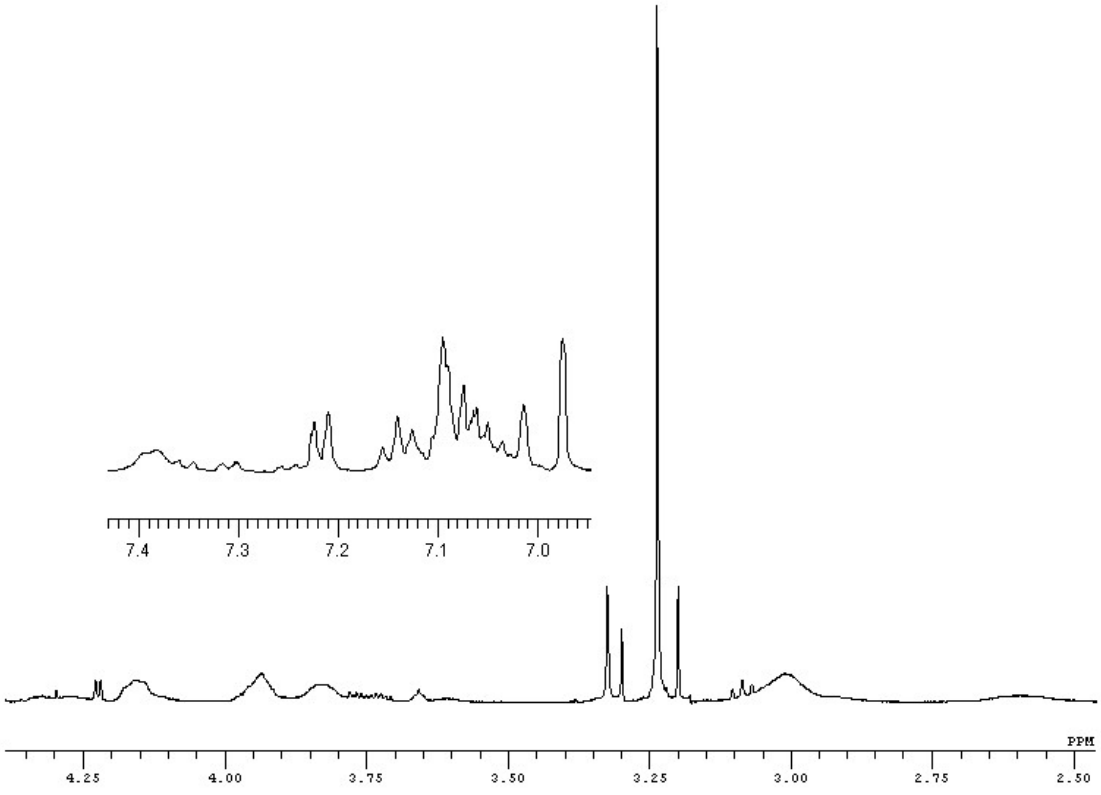


^{1}H-NMR of **17-20d** in toluene-d_8 at 20°C

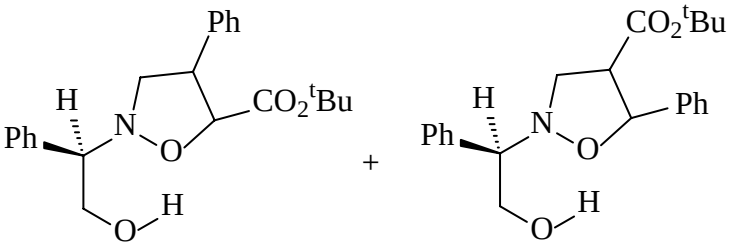


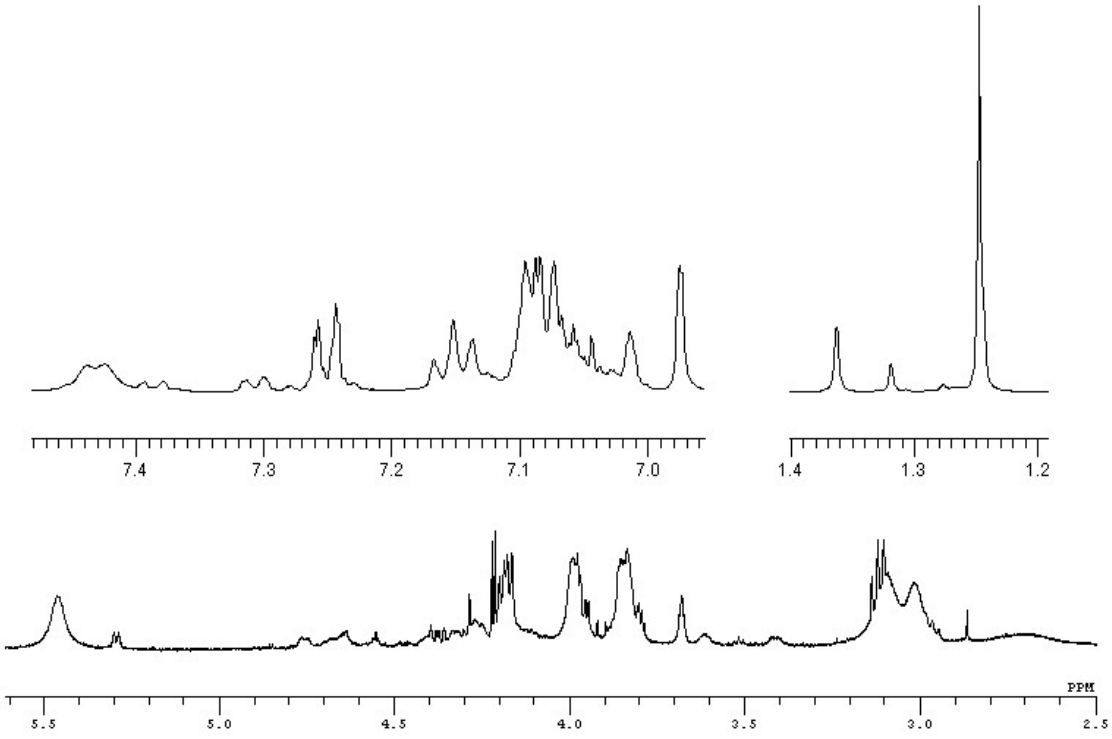
^{1}H-NMR of **17-20e** in toluene-d_8 at 20°C



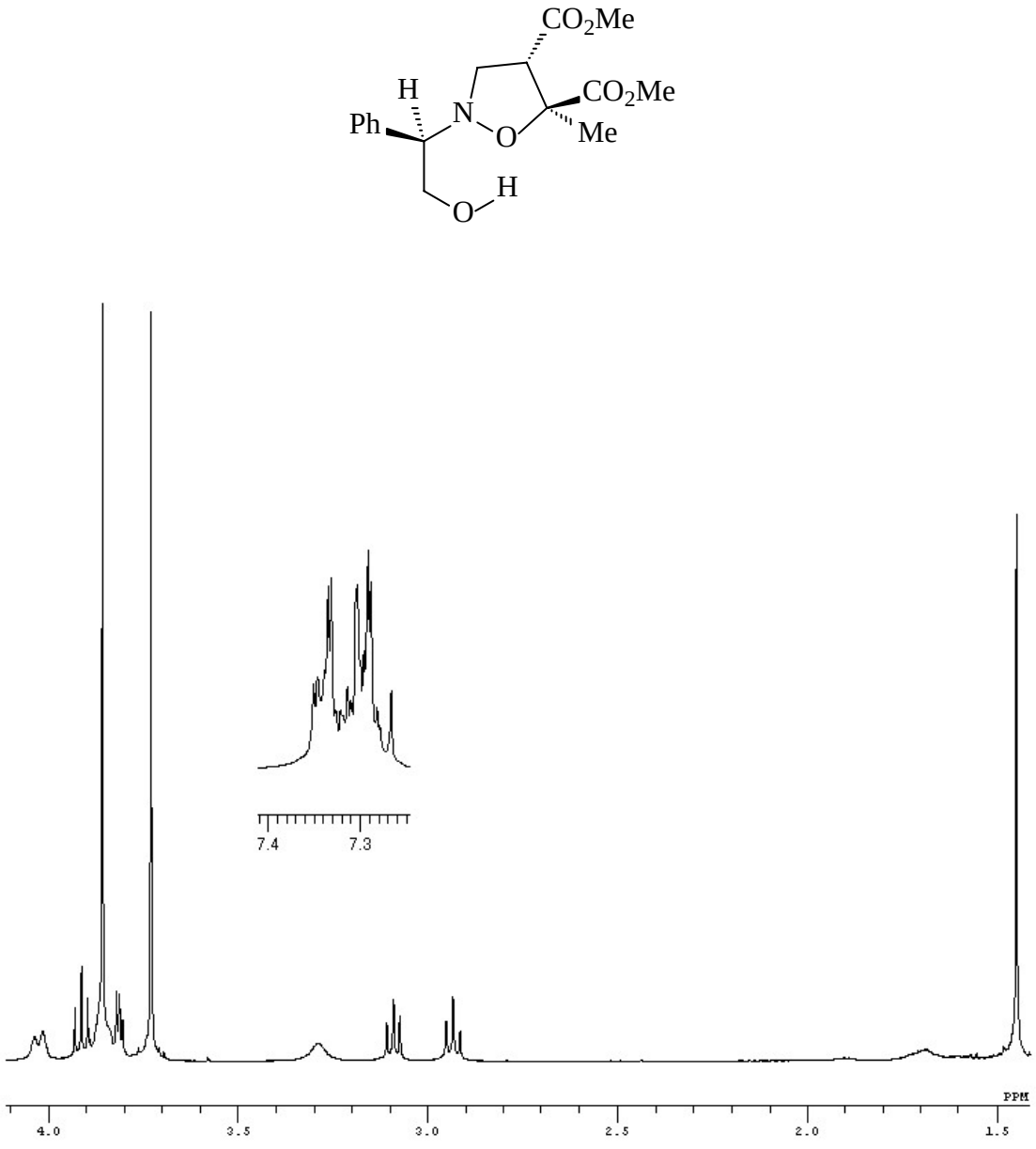


^{1}H-NMR of **17-20f** in toluene-d_8 at 20°C

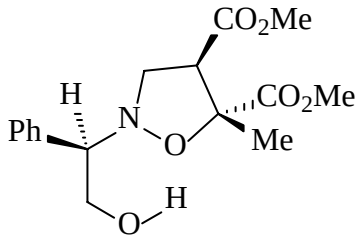


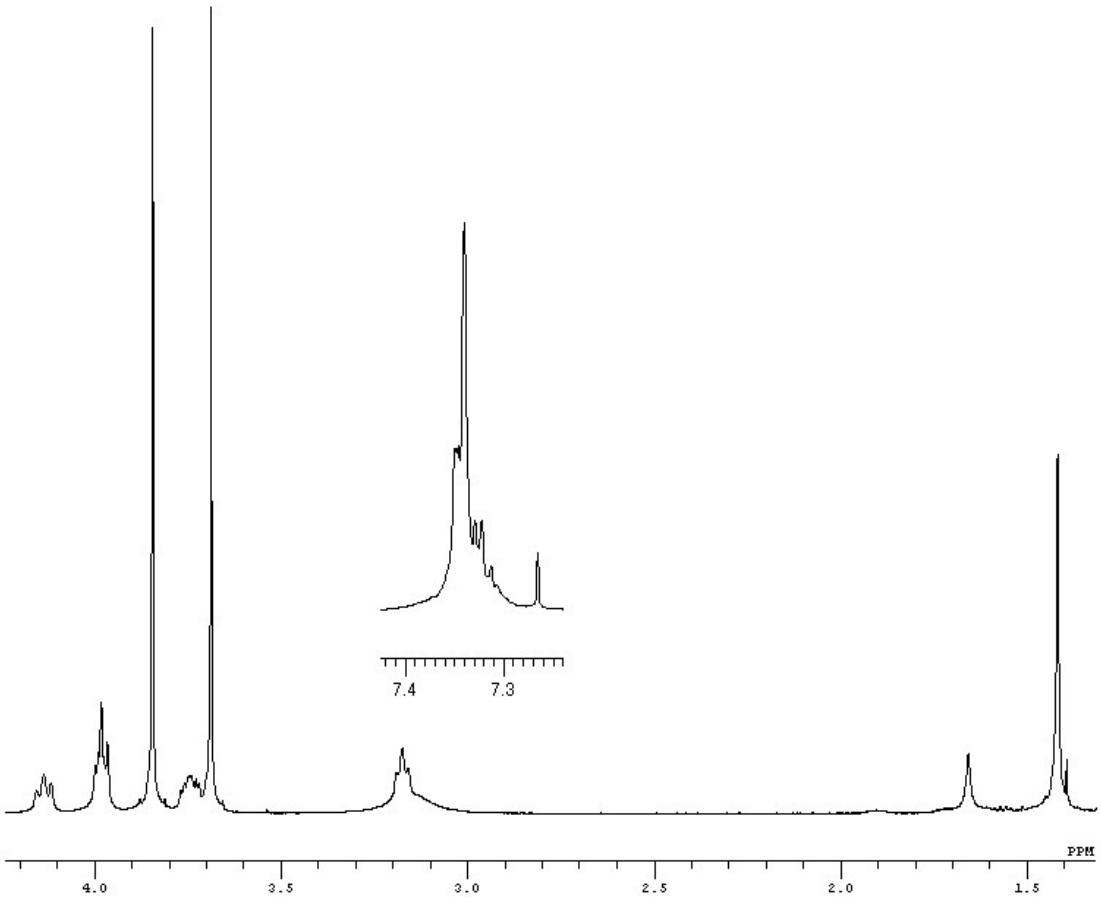


^{1}H-NMR of **17**-**20g** in toluene-d_8 at 20°C

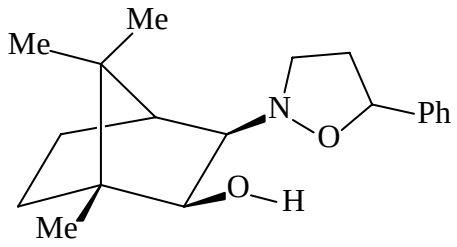


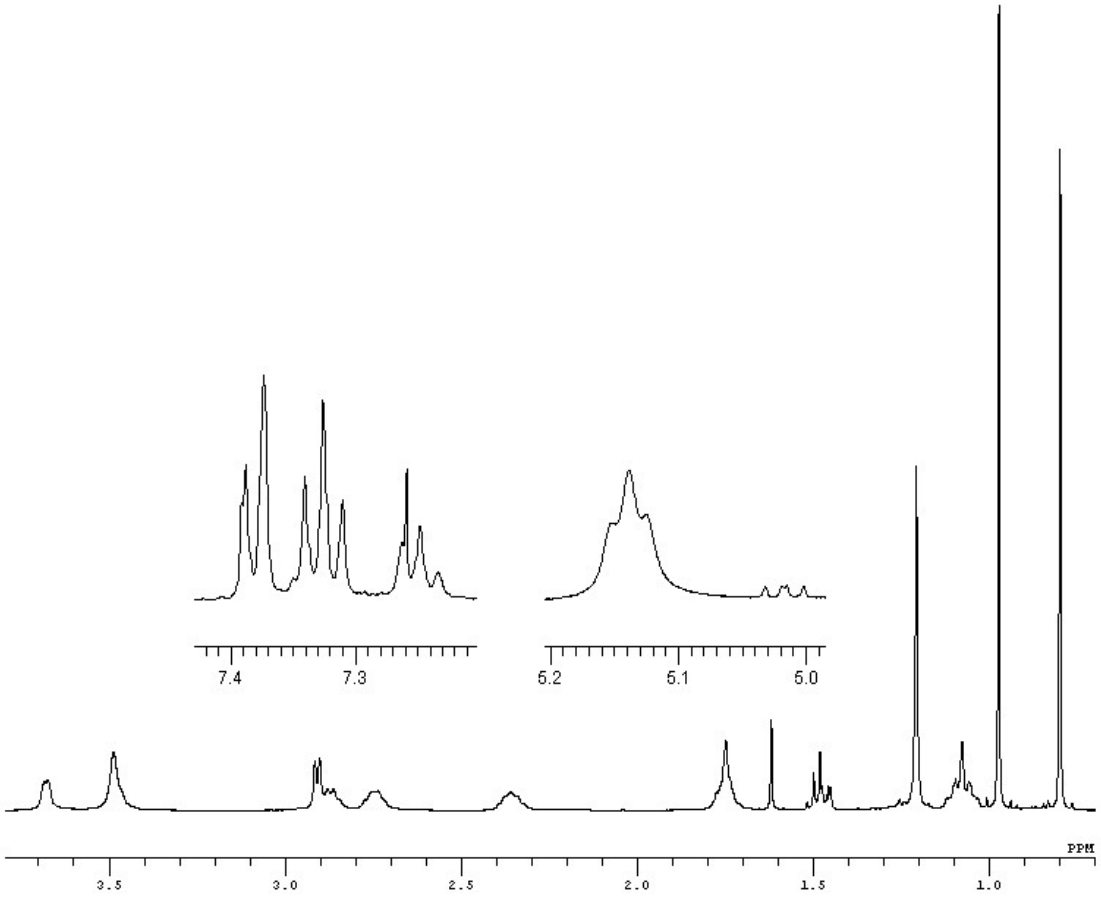
^{1}H-NMR of **165** in $CDCl_3$ at 20°C



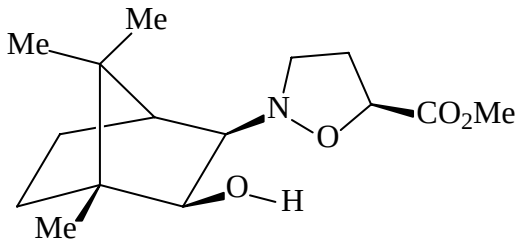


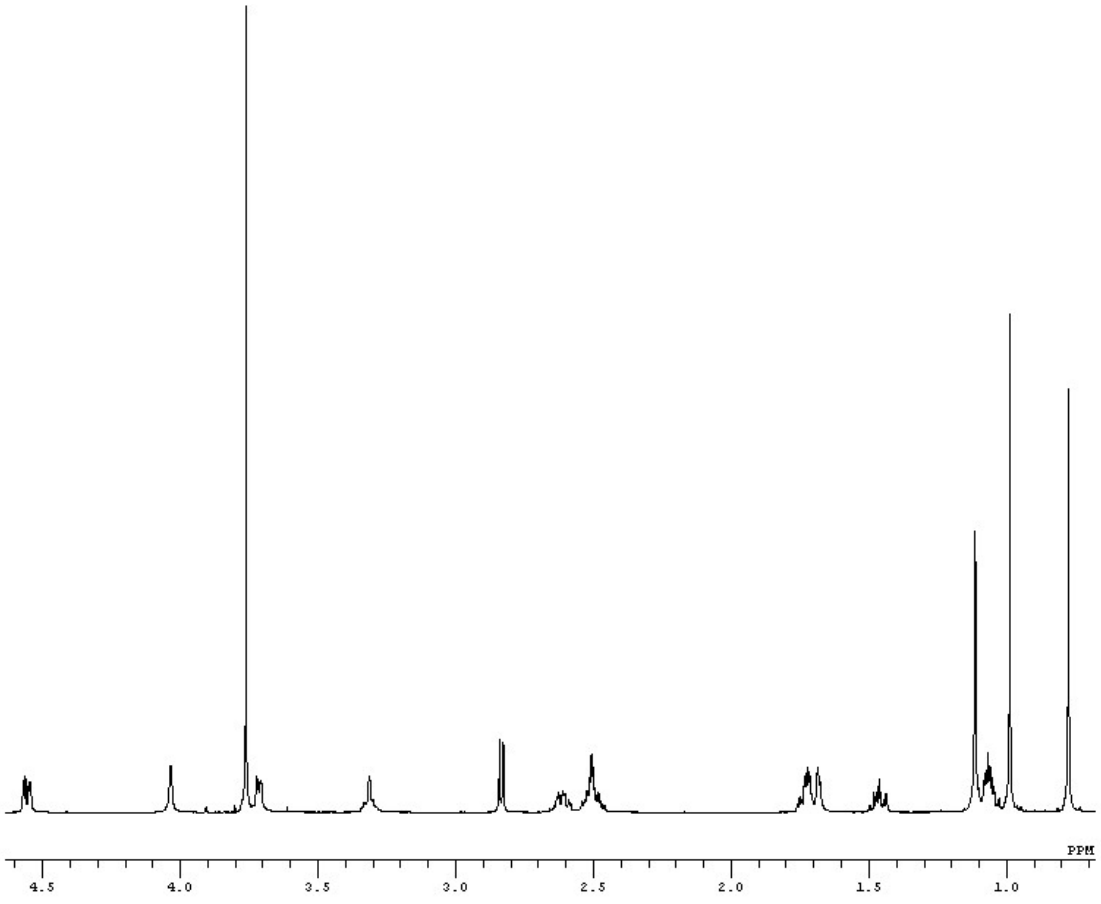
^{1}H-NMR of **164** in $CDCl_3$ at 20°C



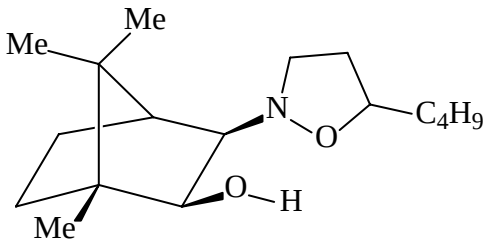


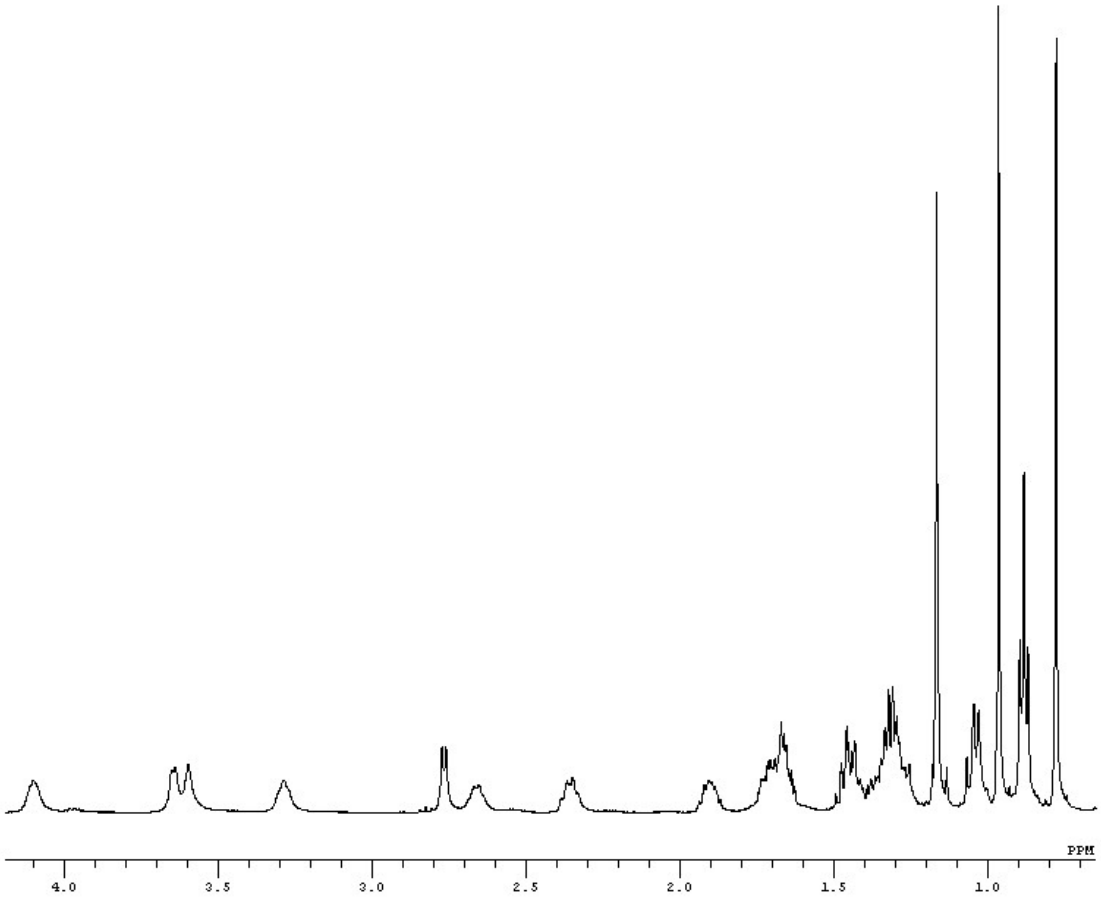
^{1}H-NMR of **22,23a** in $CDCl_3$ at 20°C



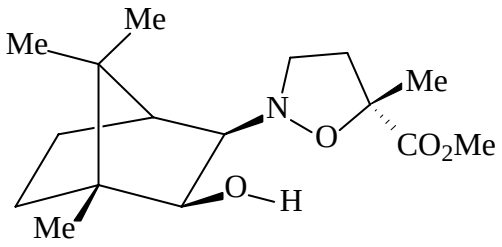


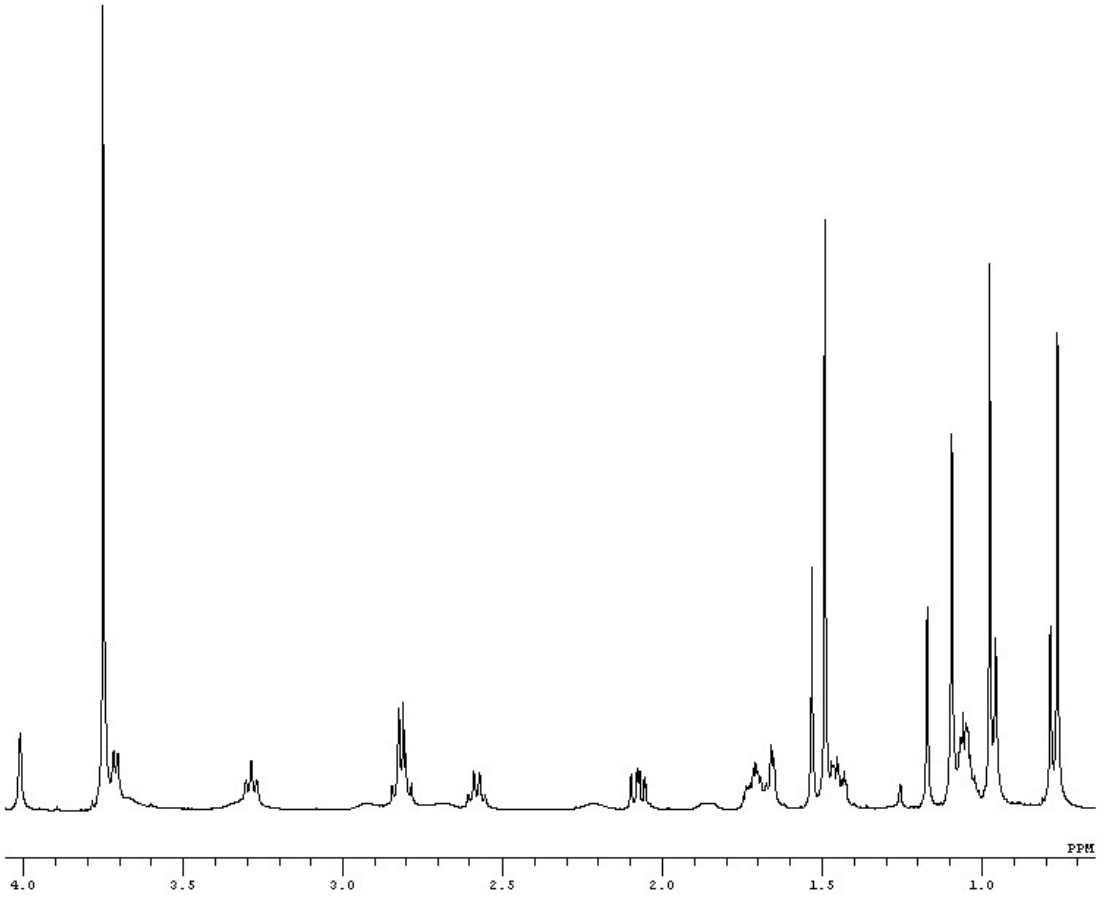
^{1}H-NMR of **22c** in $CDCl_3$ at 20°C



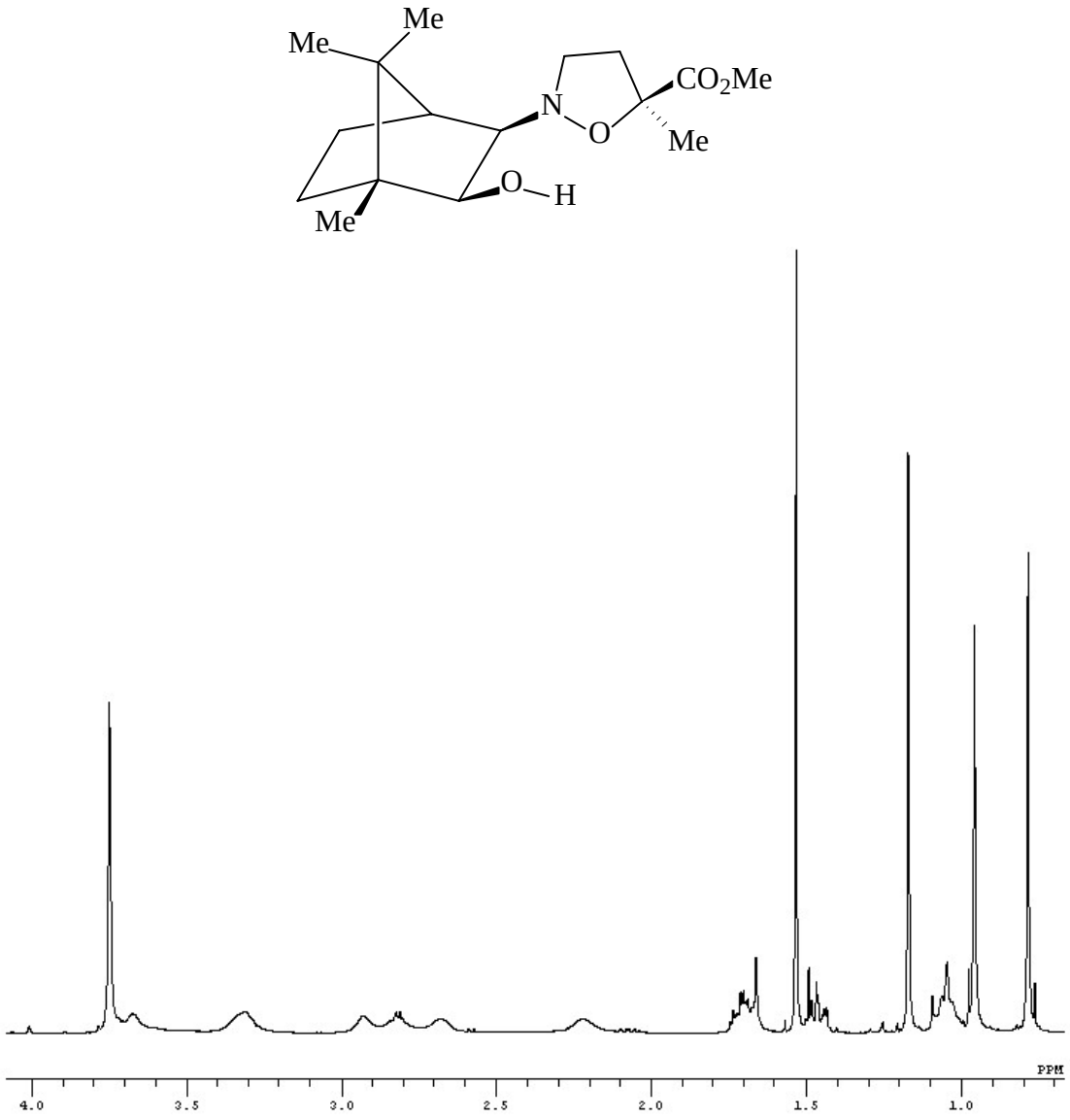


^{1}H-NMR of **22,23f** in $CDCl_3$ at 20°C

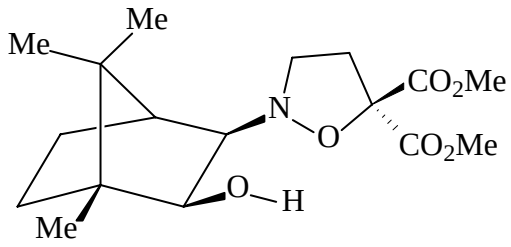


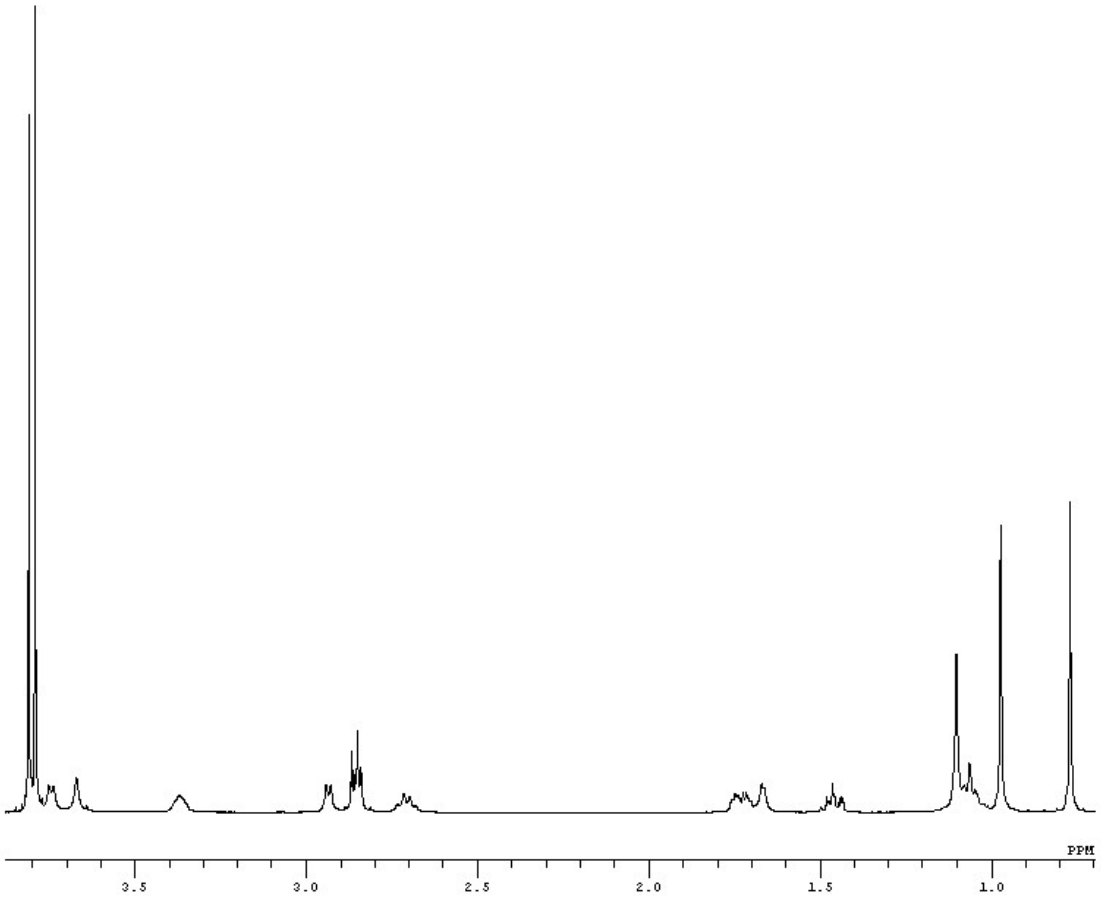


^{1}H-NMR of **25b** in $CDCl_3$ at 20°C



^{1}H-NMR of **24b** in $CDCl_3$ at 20°C





^{1}H-NMR of **24f** in $CDCl_3$ at 20°C

VITA

Muhammad Zaki Nur Iman was born in Bandung, Indonesia, on November 22nd, 1975. After getting B.S degree from Chemistry Department Institut Teknologi Bandung in October 1998, he joined Chemistry Department, King Fahd University of Petroleum and Minerals as Research Assistant in February 2004. He completed his degree in January 2006.